Topics in Atrial Fibrillation Management

ISBN: 90-8559-160-0

Cover: Anja van Rijen, Tegelen, Nederland

Financial contribution for the production of this thesis is gratefully acknowledged from the following companies and institutions

Guidant Nederland BV
Medtronic BV
Medisch Spectrum Twente
St Jude Medical Nederland BV
Stichting Hartcentrum Twente
Vitatron

Topics in Atrial Fibrillation Management

Onderwerpen uit de behandeling van boezemfibrilleren

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
Woensdag 29 maart 2006 om 13.45

door

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Geboren te Sittard

Promotiecommissie

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Voor Truus

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Chapter 1

General introduction and outline of the thesis

MF Scholten

Atrial fibrillation: "a common clinical condition"

Atrial Fibrillation (AF) has been known to man for many centuries. It was known under many different names such as delirium cordis and pulsus rirregularis pepetuus. The first recording of AF was published by Einthoven in 1906, but it was Sir Thomas Lewis who interpreted the irregular waves between the R waves as coming from the atria in his paper "Auricular Fibrillation; a common clinical condition"(1). AF is the most common sustained arrhythmia in clinical practice, with a prevalence of 1.5% in the general population(2). Its incidence increases with age, reaching 10% in the octogenarians(2). As a result, 75 % of the patients with AF are older than 75 years(3).

AF is often associated with congestive heart failure(4) hypertension, coronary heart disease, valvular heart disease and thyroid disease.

There is an increasing trend in AF prevalence and hospitalizations, illustrating the importance of AF as an economic burden and warranting effective therapy.

Atrial fibrillation: not a benign arrhythmia

AF negatively influences quality of life(5) and is associated with an increase in mortality(6, 7) especially if associated with congestive heart failure(8).

The poor prognosis of patients with AF is also known for ages. An often quoted phrase of the legendary emperor and physician Huang Ti Nei Ching Su Wen who is believed to have ruled China around 2000 BC says:

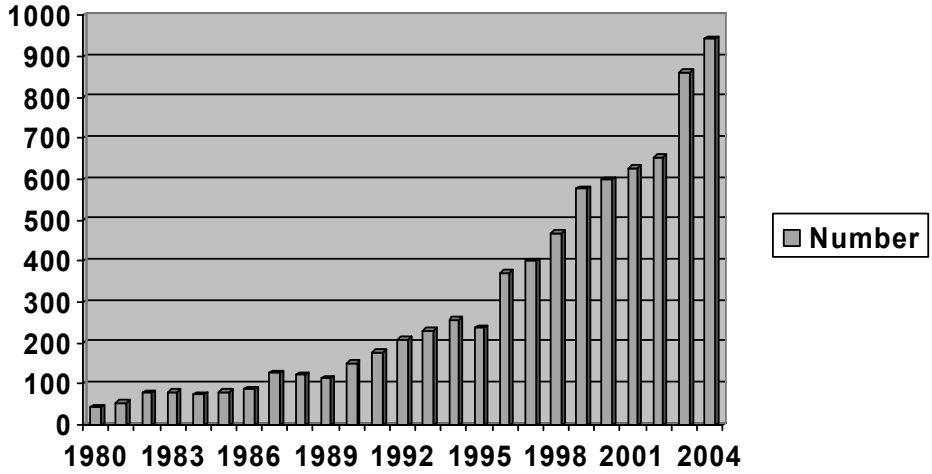
"When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades…"

Compared with the general population, the risk of a stroke is increased five-fold for patients with AF(9). The role of anticoagulation therapy against thromboembolism in patients with AF is well established as a result of several large prospective randomised controlled trials. This issue is covered in part 2 of this thesis.

The increasing interest in Atrial Fibrillation

Because of its high prevalence, it's marked effects on both mortality and morbidity and the development of effective therapies during the last decade, the interest of researchers all over the world has grown tremendously.

Number of publications found in PubMed "Atrial Fibrillation" mentioned in the Title



Atrial Fibrillation: therapeutic options

Cardioversion

The electrical cardioversion was introduced in 1962 by Lown(10). It is still the most used and effective method to restore sinus rhythm. In AF of shorter duration pharmacological cardioversion is an alternative. Part 1 of this thesis is dedicated to electrical cardioversion of AF. We compared the use of monophasic versus biphasic shock waveforms. We found no difference in efficacy, however less energy is needed using biphasic cardioversion. Transesophageal cardioversion was well tolerated in a study (chapter 3 and 4) using a modified transesopageal echocardiography probe.

Rhythm and rate control strategies

The differences between a strategy of accepting AF and adequate rate control and a strategy of maintenance of sinus rhythm (rhythm control) have been studied recently in the RACE and AFFIRM trials (11, 12). In these landmark studies no significant difference in mortality between the two strategies were found. Pharmacological rate control, however, has limited ability to mimic physiological heart rate. AV-nodal ablation and pacemaker implantation (the ablate and pace strategy) provides effective rate control and increases quality of life in symptomatic patients(13), but produces pacemaker-dependency.

The strategy of rate control is not an option for (often younger) patients with symptomatic paroxysmal AF.

Pharmacological therapy

Although not a topic of this thesis, drug therapy remains an important issue and is therefore part of this introduction. Pharmacological therapy in the treatment of AF has several goals. Drugs are used to convert AF into sinus rhythm, to maintain sinus rhythm after cardioversion, to control heart rate in permanent AF, to prevent atrial remodelling and to prevent thrombo-embolic complications .

Despite concerns about pro-arrhythmic effects drugs remain the first-line therapy for AF management. Anti arrhythmic drugs make it more difficult that multiple wavelets exist at one time (action on excitability or repolarisation).

Drugs are used to convert AF into sinus rhythm and for the maintenance of sinus rhythm after cardioversion (class 1A, 1C and III anti-arrhythmic drugs). Amiodarone is probably the most effective drug in this respect(14) and has fewer serious pro-arrhythmic complications. Its use is, however, limited because the potential of serious side effects.

AF produces changes in the electrophysiological properties of the atria that make them more vulnerable for AF(15). The decrease in atrial refractoriness (electrical remodelling) is caused by down regulation of L-type Ca-current. The potential protective role of the L-type Calcium channel blocker Verapamil after cardioversion is however not well established (16, 17).

AF can be caused by or be the cause of structural changes in the atria. Atrial stretch increases the local synthesis of angiotensin II. The level of angiotensin II and angiotensin converting enzyme are increased in fibrillating atrial tissue (18). Elevated levels of angiotensin are the cause of fibrosis formation.

Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin II (AT-II) receptor blockers have shown to decrease the recurrence rate after cardioversion (19, 20)

These studies confirmed earlier observation about the protective effects of ACEi on the development of AF after myocardial infarction(21). ACEi and AT-II receptor blockers are important adjuvant medication in the treatment of AF because they lower blood pressure, lower intra-atrial pressure and wall stress and prevent fibrosis .

Oral anticoagulation reduces the relative risk for a stroke in patients with AF by 62-70% (see chapter 6 of this thesis). Unfortunately, this therapy is still underused(22) The percutaneous left atrial appendage occluder (PLAATO) has some potential as an alternative option in those with contra-indications for the use of oral anticoagulation(chapter 5 of this thesis).

Pacemaker therapy

AF is thought to be the result of the existence of multiple wavelets or the result of fibrillatory conduction of focal activity (see chapter 8 of this thesis). Because re-

entrant tachycardias and tachycardias induced by triggered activity can be terminated by pacing or be suppressed by overdrive pacing, there is a possible role for pacemaker therapy in AF treatment. In patients with an indication for a pacemaker but without persistent AF, atrial pacing significantly reduces the incidence of AF(23, 24). This observation stimulated research in pacing prevention of AF. Furthermore it is known that bradycardia can increase the dispersion of refractoriness and thus promotes AF. In the PA3 trial DDD pacing at 70 bpm, however, failed to reduce AF recurrence rate(25). Studies using special pacing algorithms, all leading to preferential atrial pacing, showed mixed results(26).

The mechanism of preventive action of atrial pacing from alternative sites (Bachmann's bundle, interatrial septum) is thought to be the production of a more synchronous atrial activation compared with pacing from the right atrial appendage and reduces refractoriness dispersion(27). In one (small) randomised study(28) no difference in AF incidence was found between multisite pacing and standard pacing.

The disappointing results of this approach is possibly explained by the finding that septal pre-excitation prevents AF induction caused by one atrial extrasystole, but not AF induced by multiple atrial extrasystole (29). Another explanation could be the existence of other (than septal) areas of conduction delay in patients with AF.

Maze procedure

The maze procedure, developed by Cox(30), has been the most successful non pharmacological therapy for AF. The maze procedure is based on the multiple wavelet theory(31) A major disadvantage is the need for open heart surgery. However, thoracoscopic epicardial alternative procedures are being developed.

Until now, most maze procedures are done during concomitant heart surgery.

Catheter ablation

Haissaguerre et al demonstrated that in the majority of patients, AF is triggered by extrasystolic activity of the myocardial sleeves surrounding the pulmonary veins(32). These triggers became the targets of ablation therapy. A much feared complication of this procedure was pulmonary vein stenosis. The use of electro-anatomical mapping during pulmonary vein isolation proved to be of use(33). Other methods to prevent pulmonary vein stenosis is the use of cryothermal ablation (chapter 10 of this thesis) or the use of intracardiac echocardiography (chapter 14 of this thesis). Intracardiac echocardiography during pulmonary vein isolation is also of use in the titration of the ablation energy.

CONCLUSION

Much progress has been made during the last decades in the treatment of AF. Given the varied nature of AF in different patients, it seems unlikely that one therapy is suitable for all patients. Further development in pharmacological therapy, catheter ablation and surgical methods is still necessary. In this thesis attention is focused on cardioversion, anticoagulation and pulmonary vein isolation.

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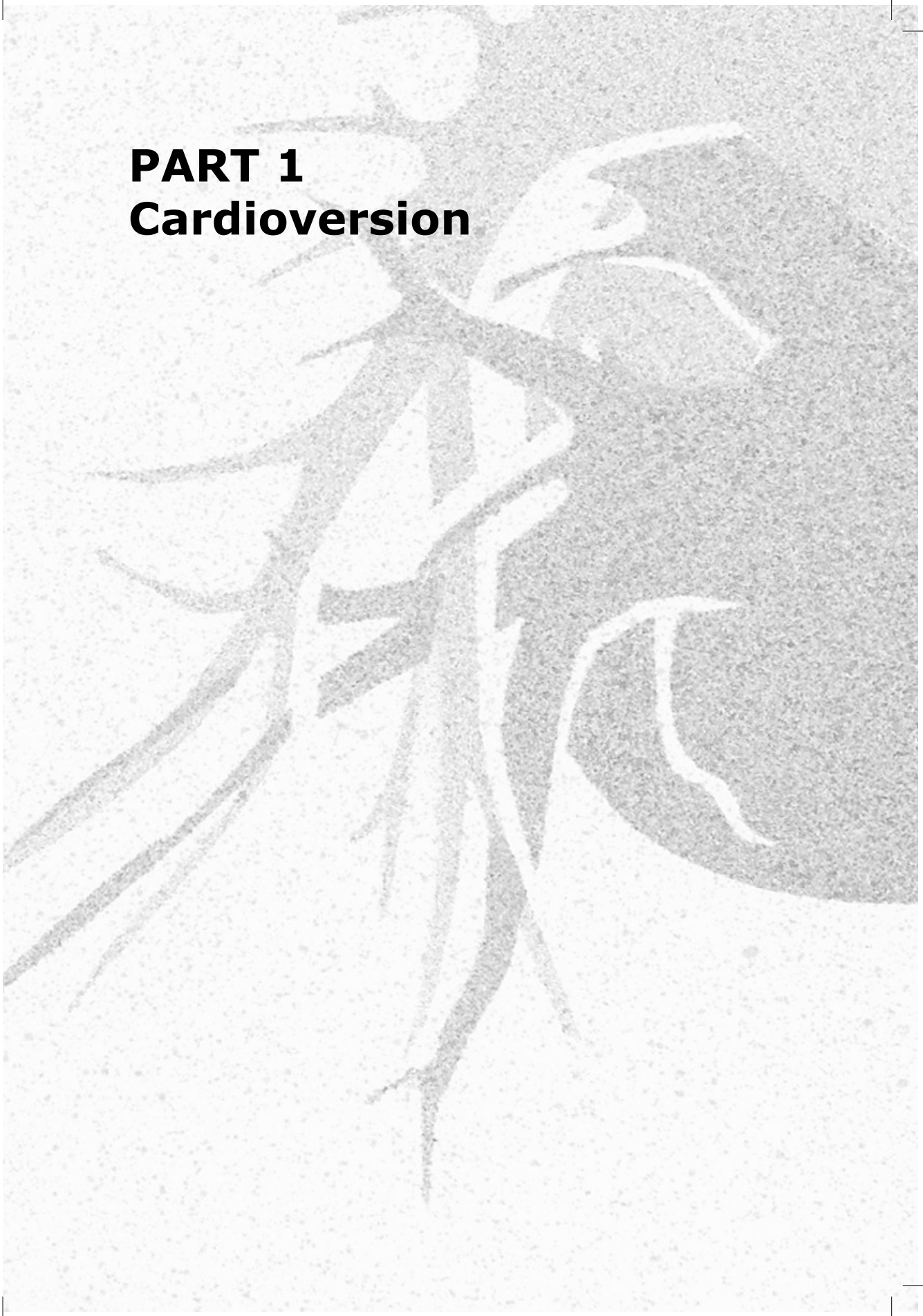

PART 1
Cardioversion

Chapter 2

Comparison of monophasic and biphasic shocks for tranthoracic cardioversion of atrial fibrillation

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Heart 2003; 89: 1-3

CARDIOVASCULAR MEDICINE

Comparison of monophasic and biphasic shocks for transthoracic cardioversion of atrial fibrillation

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Heart 2003;**89**:1–3

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Accepted 25 March 2002

Objective: To compare the efficacy of cardioversion in patients with atrial fibrillation between monophasic damped sine waveform and rectilinear biphasic waveform shocks at a high initial energy level and with a conventional paddle position.
Design: Prospective randomised study.
Patients and setting: 227 patients admitted for cardioversion of atrial fibrillation to a tertiary referral centre.
Results: 70% of 109 patients treated with an initial 200 J monophasic shock were cardioverted to sinus rhythm, compared with 80% of 118 patients treated with an initial 120 J biphasic shock (NS). After the second shock (360 J monophasic or 200 J biphasic), 90% of the patients were in sinus rhythm in both groups. The mean cumulative energy used for successful cardioversion was 306 J for monophasic shocks and 159 J for biphasic shocks ($p < 0.001$).
Conclusions: A protocol using monophasic waveform shocks in a 200–360 J sequence has the same efficacy (90%) as a protocol using rectilinear biphasic waveform shocks in a 120–200 J sequence. This equal efficacy is achieved with a significantly lower mean delivered energy level using the rectilinear biphasic shock waveform. The potential advantage of lower energy delivery for cardioversion of atrial fibrillation needs further study.

External electrical cardioversion remains the technique of choice for restoring sinus rhythm in patients with persistent atrial fibrillation.[1] Most currently used external defibrillators deliver monophasic damped sine waveform shocks. However, it has been shown that a comparable or even higher rate of transthoracic cardioversion can be achieved with biphasic shocks.[2 3] These studies assessed efficacy using step up protocols starting at low energy levels. However, 75% of the patients can be cardioverted successfully by the currently recommended 200 J initial energy level[4] using monophasic shock waveforms. Our aim in this prospective randomised study was thus to compare the efficacy of monophasic and biphasic waveform shocks for cardioversion of patients with atrial fibrillation at this initial energy level, using a conventional paddle position.

METHODS

Patient population

Two hundred and twenty seven consecutive patients were enrolled in this prospective randomised single centre study between August 2000 and January 2002. Criteria for inclusion were as follows: atrial fibrillation lasting more than 24 hours; a minimum period of medical treatment of three weeks with acenocoumarol or fenprocoumon, with an international normalised ratio (INR) of > 2.5; and absence of an intracardiac thrombus on a transoesophageal echocardiogram done within 24 hours of the cardioversion. Transthoracic echocardiograms were done in all patients within 30 days of the cardioversion in order to measure left atrial dimensions. Patients with untreated hyperthyroidism and pregnant women were excluded from the study. Patients who were cardioverted for arrhythmias other than atrial fibrillation (including atrial flutter) were not included in the analysis. Sixteen patients undergoing cardioversion for atrial fibrillation in the study period were excluded because of violation of the study protocol by the treating physician.

Protocol for cardioversion

Cardioversions were done under deep sedation using weight adjusted intravenous diazepam and ethomidate in the postabsorptive state. Randomisation was achieved on the basis of the

Table 1 Clinical characteristics of the patients

	Monophasic	Biphasic	p Value
Number	109	118	
Female (%)	24.8	25.4	NS
Age (years)	59.9 (14.0)	59.6(12.4)	NS
Height (cm)	176.4 (10.0)	177.9 (10.7)	NS
Weight (kg)	82.5 (19.8)	81.9 (20.8)	NS
Body mass index (kg/m^2)	26.5 (5.2)	26.5 (5.7)	NS
LA diameter (mm)	46.3 (8.4)	44.4 (8.9)	NS
Mean impedance (ohm)	68.5 (18.5)	80.1 (19.7)	NS
Impedance measured (n (%))	45 (41)	70 (59)	NS
Duration AF (days) (median (range))	41.0 (1–450)	20.5 (1–390)	NS
Duration AF unknown (n)	70	72	NS

Values are mean (SD) unless stated.
AF, atrial fibrillation; LA, left atrial.

Table 2 Drug treatment and underlying diseases in the patients

	Monophasic	Biphasic	
Drug treatment			
Digoxin	29 (27%)	13 (11%)	NS
Class Ic AAD	8 (7%)	13 (11%)	NS
β Blocker	18 (16%)	14 (12%)	NS
Class III AAD*	56 (51%)	75 (63%)	NS
Underlying diseases			
Valvar disease	19 (17%)	15 (13%)	NS
Lone AF	15 (14%)	25 (21%)	NS
Congestive HF	12 (11%)	11 (9%)	NS
Hypertension	12 (11%)	9 (7%)	NS
CAD	6 (6%)	5 (4%)	NS

*Sotalol or amiodarone.
AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure.

patient's birthday. Patients born on an uneven day received a 200–360 J monophasic shock sequence; patients born on an even day received a 120–200 J biphasic shock sequence. Shocks were delivered by commercially available defibrillators. The monophasic damped sine wave shock was delivered by a Hewlett Packard M1722B defibrillator (Hewlett Packard Co, Andover, Massachusetts, USA) and the rectilinear biphasic waveform by a Zoll M series biphasic defibrillator (Zoll Medical Corporation, Burlington, Massachusetts, USA). Cardioversions were undertaken using an anterolateral paddle position, and were considered successful if sinus rhythm was restored for more than five seconds. Measurement of the shock impedance was given by the defibrillator.

Statistical analysis

Variables were expressed as mean (SD) or median (range) as required. Student's *t* test was used to compare continuous variables. A χ^2 test was done for comparison of non-dichotomous variables. A probability value of $p < 0.05$ was considered significant.

RESULTS

In the study period, 359 patients were cardioverted in our department. One hundred and thirty two were excluded from the analysis either because the cardioversion was done for atrial flutter or atrial tachycardia (n = 116), or because of violation of the protocol (n = 16). Using the above mentioned selection criteria, 227 patients were enrolled into the final analysis.

The clinical characteristics of the 227 patients who fulfilled the criteria for inclusion are listed in tables 1 and 2. The monophasic and biphasic groups were similar in age, sex distribution, body weight, height, body mass index, left atrial diameter, and antiarrhythmic drug treatment. The measured shock impedance showed no difference between the two groups. Shock impedance values were not available in all patients. Information about the duration of the atrial fibrillation was also not always available. In about half the patients where data were available, there was no significant difference in shock impedance and atrial fibrillation duration between the two groups.

Monophasic and biphasic shock efficacy

The comparisons of monophasic and biphasic shock efficacy are shown in fig 1. The first shock (200 J) was successful in 77 of 109 patients (71%) in the monophasic waveform group, and in 95 of 118 patients (81%) in the biphasic waveform group. This difference was not significant ($p = 0.08$). The cumulative success of two shocks was 106 of 118 patients (91%) for the biphasic waveform group (120 J and 200 J) and 98 of 109 patients (90%) for the monophasic waveform group (200 J and 360 J). Similar efficacy was achieved with a significantly lower mean delivered energy level ($p < 0.001$) using the biphasic shock waveform (159 J) compared with the monophasic shock waveform (306 J). There were no complications related to the method of anaesthesia used. In seven patients treated with the biphasic protocol there was early recurrence of atrial fibrillation within five seconds after the first (120 J) or second (200 J) shock. In the monophasic group early recurrence of atrial fibrillation occurred in three patients. These were all considered unsuccessful results. In one patient successfully treated with the biphasic protocol, recurrence of

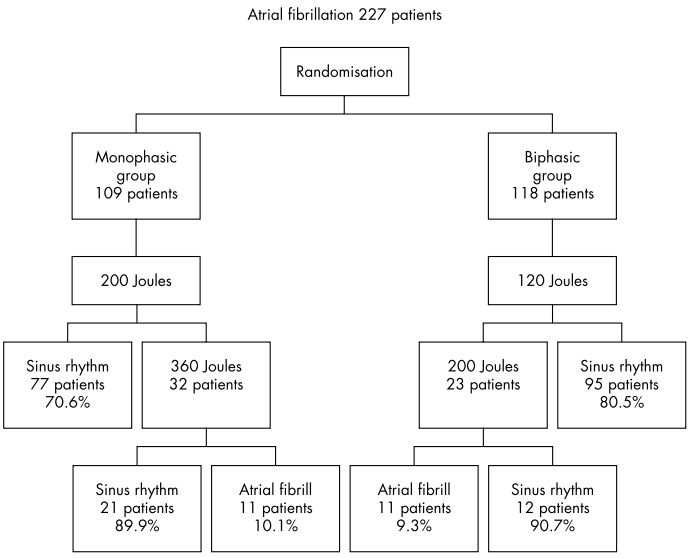

Figure 1 Study protocol and data on shock efficacy (%).

atrial fibrillation was noted after five seconds but within five minutes. This was considered as successful treatment.

DISCUSSION

In this study we could not confirm that cardioversion efficacy improves when biphasic shocks are used. The major finding of the study was that identical success rates can be achieved with monophasic and biphasic shock waveforms, selecting an initial energy level of 200 J and 120 J, respectively. As efficacy was similar with a lower delivered energy using biphasic shock waveforms, it seems necessary to investigate the potential clinical value of low energy cardioversion for patients with persistent atrial fibrillation.

Clinical value of the shock waveform

Biphasic shocks are more effective for endocardial defibrillation than monophasic shocks.[5 6] For transthoracic ventricular defibrillation, biphasic and monophasic shocks are equally effective, but biphasic shocks require less energy for the same efficacy.[7] A similar superiority for external cardioversion of atrial fibrillation has been reported recently by Mittal and colleagues using rectilinear biphasic waveform shocks.[2] Ricard and colleagues showed that for the same energy levels truncated exponential biphasic waveform shocks are superior in efficacy to monophasic waveform shocks.[3] For defibrillation of ventricular fibrillation it was found that the ST segment 10 seconds after the shock was less impaired by biphasic waveform shocks than by monophasic waveform shocks in a study that included 297 patients.[7]

Biphasic waveform defibrillation produced less impairment of cardiac function as measured by echocardiography, arterial pressure, and recurrence of heart rate in a study using mechanically ventilated pigs.[8] However, biochemical studies did not suggest any myocardial damage after cardioversion for atrial fibrillation.[3 9 10]

Selection of the initial energy level

Based on a study by Joglar and colleagues,[11] it has been recommended[12] that a 100 J monophasic shock should not be used as the initial energy level for cardioversion of atrial fibrillation because of the relatively low success rate. Current recommendations[13 14] suggest using higher initial energy levels because the success rate only becomes satisfactory at an energy level of 200 J or more (for monophasic waveforms), with a consequent decrease in cumulative delivered energy. According to the results of former studies with biphasic cardioversions, we hypothesised that a biphasic shock of 120 J may be as effective as a monophasic shock of 200 J.[3 4] Indeed this study did not show any difference in first shock efficacy and cumulative efficacy between two step protocols using monophasic (200 J and 360 J) and biphasic (120 J and 200 J) shock waveform sequences for cardioversion. The advantages of low energy cardioversion are not yet proven, but it could have an important clinical impact. Furthermore we achieved a remarkable 90% overall success rate using biphasic low energy cardioversion. This may influence further strategic planning as it could reduce the need for internal cardioversion, an effective but invasive form of treatment.

Limitations of the study

Because different defibrillators were used, the study was not double blind. The number of patients was limited but relatively large compared with previous reports. Data were not complete regarding the duration of the current atrial fibrillation episode, a known predictor of successful cardioversion. Although we clearly demonstrated that equal efficacy could be achieved with less delivered energy using biphasic shock waves, we did not attempt to assess its effect on atrial function, including differences in the development of atrial stunning.

Conclusions

For electrical cardioversion of atrial fibrillation, a protocol using biphasic waveform shocks in a 120–200 J sequence has the same efficacy as a protocol using monophasic waveform shocks in a 200–360 J sequence. This equal efficacy is achieved with a significantly lower mean delivered energy level in the rectilinear biphasic shock waveform. The potential advantages of a lower energy requirement for cardioversion of atrial fibrillation require further study in patients with persistent atrial fibrillation. However, as myocardial damage after cardioversion for atrial fibrillation has not so far been reported, there is no need for the immediate replacement of all defibrillators delivering monophasic waveform shocks.

ACKNOWLEDGEMENTS

We thank Andrew Thornton MD for reading of the manuscript and for his valuable suggestions.

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Chapter 3

Usefulness of transesophageal echocardiography using a combined probe when converting atrial fibrillation to sinus rhythm

Marcoen F. Scholten, Andrew S. Thornton, Luc J. Jordaens, Jos R. Roelandt, Richard E. Kerber and Itzak Kronzon.

Am J Cardiol 2004;94:470-473

Usefulness of Transesophageal Echocardiography Using a Combined Probe When Converting Atrial Fibrillation to Sinus Rhythm

Marcoen F. Scholten, MD, Andrew S. Thornton, MD, Luc J. Jordaens, MD, PhD, Jos R. Roelandt, MD, PhD, Richard E. Kerber, MD, PhD, and Itzhak Kronzon, MD, PhD

We studied the feasibility and efficacy of transesophageal echocardiography (TEE) combined with transesophageal cardioversion (TEC). Secondary aims were to study left atrial flow velocities before and 1 and 5 minutes after TEC, biochemical markers of myocardial damage, and patient tolerability. TEC after a short period of anticoagulation and exclusion of a clot with TEE was safe. TEC was well tolerated and efficacious. The use of a combined probe for TEE and TEC therefore can save time and be more effective. A custom-made probe for combined TEE plus TEC was used. TEC was performed with a step-up protocol (20 J to between 30 and 50 J) and with biphasic shocks. Presence of spontaneous echo contrast was scored. Cumulative energy needed to achieve sinus rhythm was calculated. Discomfort was scored on a scale of 0 to 10. Twenty-six patients underwent combined TEE/TEC. Sinus rhythm was achieved in 24 of 26 patients (92%) with a mean cumulative energy of 42.3 J. Sixteen of 26 patients were cardioverted with a 20-J shock, and 6 of these patients had early recurrence of atrial fibrillation. All biochemical markers were unaffected, and TEE/TEC was well tolerated. Left atrial appendage velocity decreased significantly after TEC. Thus, the use of a TEE/TEC probe offers effective cardioversion with low energy levels, is well tolerated, and hemodynamics during and immediately after cardioversion can be monitored. Early cardioversion after exclusion of a clot with this combined probe is time saving and cost effective.
(Am J Cardiol 2004;94:470–473)

Transesophageal cardioversion (TEC) has been studied previously and is safe and efficacious.[1–3] Combining transesophageal echocardiography (TEE) for exclusion of a thrombus with TEC has the potential benefit of using 1 administration for sedation and offers the opportunity to study left atrium and left atrial appendage (LAA) flow phenomena during and immediately after cardioversion.

METHODS

Study design: We evaluated the efficacy and feasibility of TEE combined with TEC. A secondary aim of the study was to observe changes in atrial function and flow velocities and to measure biochemical parameters of myocardial damage after cardioversion. The study was approved by the institutional medical ethics committee, and written informed consent was obtained from all patients.

Patients: Patients were enrolled in the study if they had atrial fibrillation lasting >24 hours, were >18 years old, and were willing to provide informed consent. Patients with gastrointestinal pathology that did not permit the use of TEE were excluded.

Anticoagulation: To prolong prothrombin time to an international normalized ratio of 2 to 3, patients were treated for ≥4 days with acenocoumarol or fencoumadin. If there was a need for immediate cardioversion, a continuous infusion with heparin was started after a bolus injection before cardioversion to prolong the activated partial thromboplastin time ratio to between 2 and 3. Administration of acenocoumarol was begun at the same time. Heparin was continued until the international normalized ratio was between 2 and 3.

Transesophageal echocardiography: TEE was performed using commercially available equipment (Sonos 5500, Philips Medical Systems, Eindhoven, The Netherlands). LAA flow was measured with the sample volume 1 cm from the LAA orifice. Maximal atrial emptying velocity before cardioversion and early diastolic emptying velocity after TEC were measured. Spontaneous echo contrast was classified as absent or present; if present, echo contrast was graded as 1 (limited to LAA), 2 (weak signal seen in the left atrium and LAA), or 3 (dense swirling in the left atrium and LAA). For this study, we used a locally customized standard TEE probe (Agilent model 21364R, Philips Medical Systems) plus 2 titanium electrodes that were each 110 mm^2. After each procedure, the probe was sterilized with 70% ethanol, according to health authority regulations for probes.

Transesophageal cardioversion: All patients were treated during a postabsorptive state after application of

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TABLE 1 Patient Characteristics

Patient No.	Age (yrs)/Sex	LAD (mm)	BMI (kg/m^2)	Antiarrhythmic Drug	Diagnosis
1	53 M	51	32.51	Verapamil	Valve
2	54 M	51	25.00	Disopyramide	Valve
3	65 M	55	24.62	Amiodarone	Valve
4	67 F	46	33.73	Verapamil	Valve
5	68 M	42	29.03	Verapamil	Valve
6	70 F	45	25.61	Amiodarone	Valve
7	77 M	50	28.73	Metoprolol	CAD/valve
8	51 M	42	24.31	Sotalol	CAD
9	64 F	46	29.02	Bisoprolol	CAD
10	65 M	43	28.73	Digitalis	CAD
11	80 M	43	21.30	0	CAD
12	65 M	47	25.25	Flecainide	Hypertension
13	71 F	48	26.03	0	Hypertension
14	65 M	48	33.91	0	Hypertension
15	74 M	49	23.74	0	Hypertension
16	65 M	42	21.61	Metoprolol	Lone AF
17	55 M	43	26.87	Amiodarone	Lone AF
18	37 M	47	33.08	Amiodarone	Lone AF
19	79 F	48	40.39	Amiodarone	Lone AF
20	69 M	49	33.41	Digitalis/verapmil	Lone AF
21	45 M	56	26.59	Digitalis/verapamil	Lone AF
22	54 M	58	31.25	Amiodarone	Lone AF
23	60 F	72	29.62	Amiodarone	IDC
24	75 M	40	27.04	Amiodarone	IDC
25	66 M	45	25.93	0	IDC
26	49 F	56	21.45	Amiodarone	CHD

AF = atrial fibrillation; BMI = body mass index; CAD = coronary heart disease; CHD = congenital heart disease; IDC = idiopathic dilated cardiomyopathy; LAD = left atrial dimension assessed with echocardiography; M = male; valve = valvular disease.

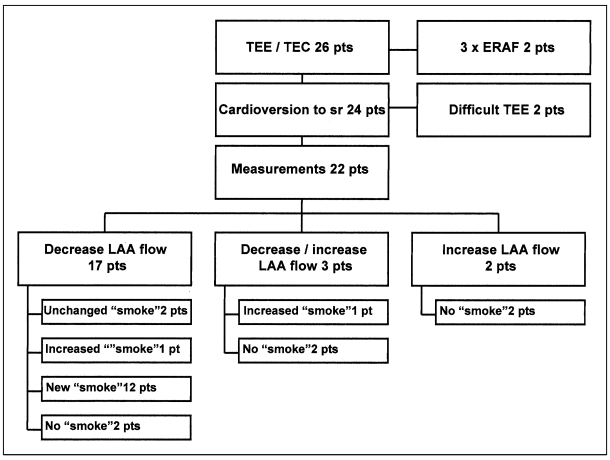

FIGURE 1. Spontaneous echo contrast is also known as "smoke." In 4 patients (pts), echo measurements were incomplete because of repeated early recurrence of atrial fibrillation (ERAF) or difficulties in performing TEE. Most patients showed a decrease in LAA flow velocity. Three patients showed an increase in LAA flow velocity 5 minutes after an initial decrease. Only 2 patients showed unchanged or increased LAA flow velocity.

topical anesthesia of the hypopharynx with 1% lidocaine spray. Before TEE, patients were sedated with 5 mg of diazepam intravenously. If no thrombi were seen in the left atrium or LAA, cardioversion was performed after a weight-adjusted dose of etomidate.[4] Blood pressure, oxygen saturation, and heart rhythm were continuously monitored. Biphasic R-wave synchronous shocks were delivered with a Zoll M-series biphasic defibrillator (Zoll Medical Corp., Burlington, Massachusetts) between the electrodes on the transesophageal probe and a midsternal patch of 63.6 mm^2 (Zoll Pro-padz, Zoll Medical Corp.). A step-up protocol from 20 J to between 30 and 50 J was used. Early recurrence of atrial fibrillation was defined as recurrence of atrial fibrillation after cardioversion to sinus rhythm within 1 minute.[5] In case of early recurrence of atrial fibrillation, another shock at the same energy level was given. All patients were hospitalized and monitored ≥6 hours.

Patient discomfort: Patient discomfort caused by the TEE was expressed on a scale from 1 (no discomfort) to 10 (maximal discomfort).

Biochemical markers: Cardiac enzymes (creatine kinase, creatine kinase-MB fraction, myoglobulin, and troponin-T) were measured hourly ≥6 hours after cardioversion.

Outcomes: Primary outcome of the study was energy requirement for restoration of sinus rhythm. Secondary clinical outcomes were echocardiographic assessment of the left atrium and LAA function, measurement of cardiac enzymes, and indexes of patient comfort and potential esophageal complaints using a questionnaire.

RESULTS

Patients: Patient characteristics are listed in Table 1. Twenty-six patients (7 women; mean age 63 years, range 37 to 80; mean body mass index 27.92 kg/m^2, range 21.30 to 40.39, SD 4.49) were included in this study. Duration of atrial fibrillation was unknown in most patients. Mean left atrial diameter measured with transthoracic echocardiography was 48.5 mm (range 40 to 72, SD 6.77).[6]

Cardioversion energy: Cardioversion of atrial fibrillation into sinus rhythm was successful in 24 of 26 patients (92%). Sixteen of 26 patients were cardioverted to sinus rhythm with one 20-J shock, and 6 of these patients had early recurrence of atrial fibrillation and were cardioverted again once (n = 3) or twice (n = 3) with

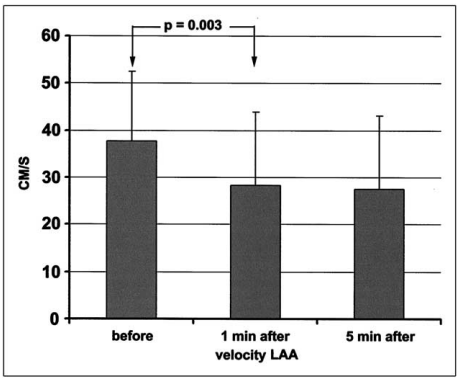

FIGURE 2. Mean LAA velocity measured by pulse-wave Doppler echocardiography before and 1 and 5 minutes after cardioversion. Values are expressed as centimeters per second and as mean ± SD.

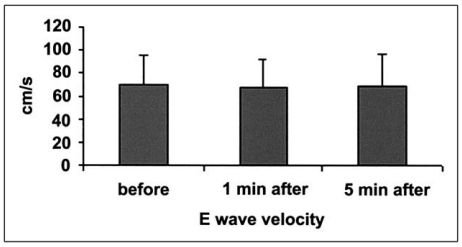

FIGURE 3. Mean transmitral E-wave velocity measured by pulse-wave Doppler echocardiography before and 1 and 5 minutes after cardioversion. Values are expressed as centimeters per second and as mean ± SD. E = contribution of early filling phase to transmitral flow.

20 J. Two of these 3 patients had another early recurrence, and further cardioversion was not attempted. Eight of 26 patients were cardioverted to sinus rhythm with 2 shocks (20 to 30 J), and 2 of 26 patients were cardioverted with 3 shocks (from 20 to between 30 and 50 J). Mean cumulative shock energy, including repeated shocks for recurrence of atrial fibrillation or for failure to achieve sinus rhythm, was 42.32 J (range 20 to 100). Mean first shock impedance was 129 Ω (range 86 to 150).

Patient comfort: TEE/TEC was performed in all patients who signed informed consent. Patient discomfort was caused mainly by TEE. Mean discomfort rate was 2.15 (range 0 to 6, SD 1.66). One patient temporarily complained about a sore throat. No patient had objections against a repeated procedure, if required.

Echocardiographic measurements: No clot in the left atrium or LAA was seen. Echocardiographic measurements were done in the 24 patients successfully cardioverted to sinus rhythm (Figure 1). In the 2 patients in whom treatment was unsuccessful, measurements were incomplete because all attention was paid to the repeat TEC. Mean LAA flow decreased over time (Figure 2), whereas mean early diastolic transmitral flow (E wave) remained unchanged (Figure 3). In 3 patients, spontaneous echo contrast was present before TEC; in 2 of these patients, intensity of spontaneous echo contrast increased from grade 1 to 2 and from grade 2 to 3, respectively, after TEC. In 12 patients, spontaneous echo contrast appeared after cardioversion, and the intensity of this spontaneous echo contrast increased over time. This observation paralleled the decreased flow velocity in the LAA, because all patients showed spontaneous echo contrast of LAA flow that decreased over time.

Biochemical markers: No increase in parameters of myocardial injury was measured.

DISCUSSION

Early cardioversion after exclusion of atrial thrombi by TEE is an established method.[7] TEE before cardioversion is also recommended in a subgroup of patients with a higher risk for thromboembolic events despite the use of anticoagulation. The presence of spontaneous echo contrast in the left atrium identifies a subgroup of patients with atrial fibrillation at an increased risk of thromboembolism.[7,8] Low velocities in the LAA before cardioversion are important markers for recurrence of atrial fibrillation.[9] TEC is a safe, alternative approach for cardioversion and requires considerably less energy than transthoracic cardioversion.[3] Systematically performed endoscopic studies after TEC in animals and humans have shown that damage to the esophagus is very rare and that any damage heals spontaneously.[2,10] We report the first clinical experience of TEE plus TEC by using a biphasic shock wave. A notable number of patients (6 of 26) showed early recurrence of atrial fibrillation after a 20-J shock. No early recurrence of atrial fibrillation was seen after a 30- or 50-J shock. Because of the small number of patients and the unknown duration of atrial fibrillation, conclusions cannot be drawn. Our echocardiographic observations confirm those of previous studies that reported low atrial velocities after cardioversion for atrial fibrillation or atrial flutter.[11–13] The finding of stunning in the left atrium and LAA (decreased flow velocity and spontaneous echo contrast) may predict thrombosis and underlines the necessity for anticoagulation after electrical cardioversion. It is of note that this stunning occurred despite the use of very low energy for cardioversion. The observed stunning has been postulated to be related to the duration of atrial fibrillation.[14] The stunning of the left atrium and LAA probably extended our observation period, because low velocities in the LAA have been found 24 hours after cardioversion.[15] Remarkably low energy was required, and the procedure was very well tolerated by the patients. The mean interval between the decision for cardioversion and TEC was 3.4 days (range 1 to 11), so our goal of early cardioversion after the diagnosis of atrial fibrillation was reached. No gastrointestinal complaints after the procedure were noted, except a temporary sore throat in 1 patient.

Acknowledgment: We are indebted to Petter Janse, Richard Alloway. and the other nursing staff. Without their support and work, this study would have been impossible.

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Chapter 4

Combined transesophageal echocardiography and transesophageal cardioversion probe: Technical aspects

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J Am Soc Echocardiography 2005; 18:213-5

Combined Transesophageal Echocardiography and Transesophageal Cardioversion Probe: Technical Aspects

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A probe assembly for simultaneous transesophageal echocardiography and transesophageal cardioversion has been developed. This probe allows cardioversion with the delivery of much lower energy than the standard external approach. Details of the probe construction and its use are described, as is the prospect for future practice. The use of a combined probe may be the technique of choice for patients who require both cardioversion and transesophageal echocardiography. (J Am Soc Echocardiogr 2005; 18:213-5.)

There are currently two approaches to elective direct current cardioversion of atrial fibrillation. The conservative approach entails 3 weeks of precardioversion anticoagulation, in addition to postcardioversion anticoagulation. More recently, patients have undergone immediate cardioversion after acute heparinization (without 3 weeks of preceding anticoagulation) in the absence of thrombi in the heart on transesophageal echocardiography (TEE). This latter approach has been shown to be equally effective in preventing strokes, and is associated with fewer bleeding complications (because of the shorter duration of anticoagulation).[1] Consequently, the TEE-guided method has gained popularity and is used by many institutions as their primary approach to elective cardioversion.

The logistics of the TEE-guided approach are somewhat complex, and may require evaluation of the patient by two separate teams (from the echocardiography and electrophysiology laboratories). Furthermore, two separate periods of conscious sedation are often necessary, with the patient being transported from one site to another. The guidelines for the TEE-guided approach have not been fully established.

Transesophageal cardioversion (TEC) has been described,[2] and has been used in hundreds of patients. For this procedure, an electrode (E) is inserted into the esophagus and placed behind the heart. The other E is placed on the anterior chest wall. Because of the proximity of the esophageal E to the heart, a lower energy level can be used and cardioversion can be achieved with 50 J or less in most patients. The procedure is safe, and no damage to the esophagus is noted when less than 100 J is used for cardioversion.

Because TEC is considered semi-invasive, it did not achieve great popularity. However, recently the advent of TEE for precardioversion diagnostic purposes has made esophageal intubation commonplace. We, therefore, thought that using a modified TEE probe both for imaging and cardioversion made sense. Our initial experience with combined TEE and TEC has been recently described.[3] Cardioversion could be successfully performed in 92% of patients using an energy level of 20 to 50 J, and there were no complications. In the current report the details of the design of the combined TEE/TEC probe assembly will be described, with procedural considerations, and prospects for future improvements in both the apparatus and technique.

METHODS

The Probe

As shown in Figure 1, a commercially available TEE probe was modified. Two titanium Es (110 mm^2 each) were mounted one next to the other just proximal to the TEE imaging transducer at the tip of the probe, with the Es facing in the same direction as the imaging transducer (the Es are in contact with the esophagus). The combined size of the two Es was approximately the same size as the transducer head. The Es are interconnected, and a connecting (C) wire is wrapped around the shaft of the probe.

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0894-7317/$30.00

doi:10.1016/j.echo.2004.12.010

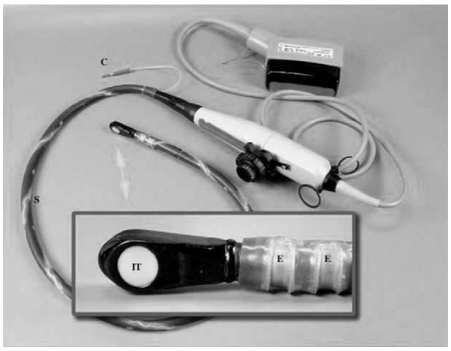

Figure 1 Commercially available transesophageal echocardiography probe has been modified for transesophageal cardioversion. *C*, Connecting wire (to cardioversion device); *E*, titanium electrodes; *IT*, imaging transducer; *S*, silicone rubber insulation over wire wrapped around probe; *yellow arrow*, magnified view of tip of probe (*blue outlined frame*).

The entire probe is covered with silicone rubber, which insulates the C wire and makes the surface of the shaft smooth. The surface of the two Es is left uncovered and the end of the wire is C with one of the output contacts of a standard cardioversion apparatus. The second E is placed on the patient's chest and C to the other output contact of the cardioversion apparatus. Thus, instead of two Es on the chest wall used for standard cardioversion, there is one E on the chest wall and another on the TEE probe. The TEE/TEC probe can be sterilized in routine fashion (eg, with Cidex [Johnson & Johnson, Irvine, Calif] or 70% alcohol).

Safety Issues

TEC using an intraesophageal E has been shown to be safe. However, to further explore the safety of the TEE/TEC probe, we used it in 4 mongrel dogs. The TEE/TEC probe was placed in the esophagus behind the left atrium (LA), and its position was confirmed by imaging. A second E was placed on the chest wall. A shock of 50 or 100 J was delivered. All of the dogs were killed 1 hour (two dogs) and 24 hours (two dogs) after the shock. The esophagus was examined both macroscopically and microscopically by a gastrointestinal pathologist. No significant damage to the esophagus was found. Based on previous experience with TEC (without imaging) and our experience in dogs, the use of TEE/TEC was approved for a human trial by the institutional review board of the Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands. The mean shock impedance was 129 Ω (range 86-150). This experience made esophageal damage unlikely.

Patients with esophageal pathology such as varices, diverticulae, and tumors are not candidates for TEE or TEE/TEC. Because of the effects of TEC on the esophagus of patients with symptoms of esophagitis, we would not recommend this procedure for such patients.

We did not experience any serious arrhythmias in our patients. However, should a severe arrhythmia ensue during the procedure (eg, ventricular tachycardia or fibrillation) we would not recommend using the probe for treatment, but would rather proceed with standard external cardioversion under these circumstances. If there is a life-threatening bradyarrhythmia, transesophageal pacing through the TEE/TEC probe can be easily performed.

Study Protocol

This has been previously described in detail.[3] Briefly, the TEE/TEC probe was used in 26 patients who were considered to be candidates for both TEE and cardioversion. All patients were effectively anticoagulated at the time of the cardioversion, and for at least 6 weeks thereafter. Biphasic R-wave synchronous shocks were delivered after sedation, with a step-up protocol from 20 to 50 J. If there was an early recurrence of atrial fibrillation (within 1 minute of the low-energy shock) a shock 10-J higher was delivered. A complete TEE study was obtained before the cardioversion, with special emphasis on the detection of intra-atrial anatomy, and the presence or absence of thrombi or spontaneous echocontrast. Pulsed wave Doppler measurement of transmitral and LA appendage flow were recorded and analyzed. Continuous imaging was obtained for 5 minutes after cardioversion and transmitral and LA appendage flow parameters were recorded and analyzed, until the probe was removed.

RESULTS

The first TEC using TEE/TEC was performed at the study center on March 13, 2003 (Figure 2). None of the 26 patients had an atrial thrombus, and 24 patients (92%) were successfully cardioverted to normal sinus rhythm. In 16 of these 24 patients, a single shock of 20 J was sufficient. The mean cumulative energy used for the 24 patients was 42 J.[3] Postcardioversion, there were more signs of blood stasis seen; there was more spontaneous echocontrast and a lower LA appendage emptying velocity than before the cardioversion. These findings confirm previous observations consistent with atrial stunning,[4] and emphasize the need for postcardioversion anticoagulation. There were no complications, no elevation of creatine phosphokinase, and no gastrointestinal symptoms (dysphagia or heartburn).

DISCUSSION

The state of the art for electrical cardioversion requires precardioversion TEE in many patients to exclude thrombus, and to define the prognosis for the maintenance of normal sinus rhythm. Acute

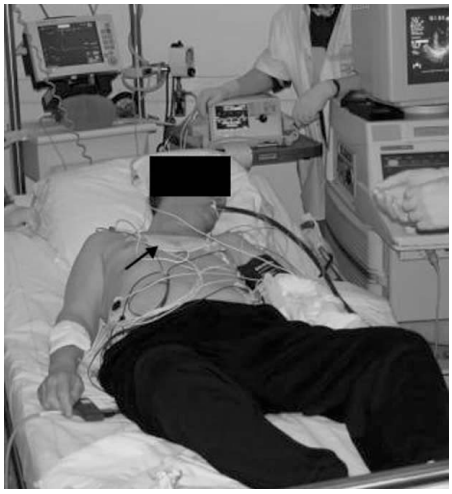

Figure 2 First transesophageal echocardiography (TEE)/cardioversion procedure, March 13, 2003. Electrode on patient's chest (*arrow*). Technician behind patient is operating cardioversion device, which is connected to TEE probe and chest electrode.

cardioversion, with prior TEE to rule out intracardiac thrombi, avoids a delay of weeks for anticoagulation. This delay results in a longer period of atrial fibrillation, which may reduce the chance of maintaining in sinus rhythm after cardioversion ("atrial fibrillation begets atrial fibrillation").

It has been shown that precardioversion LA appendage velocities of more than 40 cm/s are associated with a higher likelihood of maintaining NSR after 1 year.[5] The combined TEE/TEC probe appears to be the ideal tool for performing both imaging and cardioversion. The proximity of the probe to the LA allows for a lower energy delivery for cardioversion, and consequently there is no skin burn (which is often seen with transthoracic cardioversion) and no elevation of creatine phosphokinase (caused by skeletal muscle trauma during standard cardioversion). In addition, it can give information about the immediate postcardioversion hemodynamics and may predict potential complications of the procedure (eg, thrombus formation). The procedure is safe and well tolerated. This technique also allows for both transesophageal imaging and cardioversion to be done with one episode of sedation, in the same location, thus, improving patient comfort and safety, and reducing costs.

Future Prospects

Transesophageal probes can be easily modified to perform TEE/TEC. However, this alteration to the TEE probe may not be necessary. A sheath can be designed that contains the E and the C wire. Any TEE probe could be inserted into the sheath, making a combined instrument without permanently altering the probe. A multicenter study of TEE/TEC should be considered, but our preliminary observations suggest that this approach may be the technique of choice for patients that require both TEE and cardioversion.

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PART 2
Prevention of thromboembolic events

Chapter 5

First Dutch experience with percutaneous left atrial appendage transcatheter occlusion

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Neth Heart Journal 2003;11:506-9

First Dutch experience with percutaneous left atrial appendage transcatheter occlusion

M.F. Scholten, L.J. Jordaens, P.A. Cummins, P.W. Serruys

Background. **Patients with atrial fibrillation (AF) have an increased risk of thromboembolic stroke, dependent on clinical variables. Oral anticoagulation significantly decreases the risk of stroke or embolism, but sometimes this is difficult to manage and may be contraindicated. Approximately 90% of atrial thrombi in nonrheumatic AF are found in the left atrial appendage (LAA). A new device has been developed which allows percutaneous LAA occlusion (PLAATO) and might be an alternative to oral anticoagulation. Feasibility in dogs and humans was described previously.**
Methods and Results. **As part of an international multicentre trial, three patients received a percutaneous transcatheter LAA occlusion device. Implantations were performed without general anaesthesia, guided by intracardiac and transoesophageal echocardiography and without major complications. The implantations were well tolerated by the patients, who entered a long-term follow-up to be compared with a historical control group.**
Conclusion. **Transseptal percutaneous LAA occlusion is feasible. Its role as an alternative to oral anticoagulation, however, needs to be further defined. (*Neth Heart J* 2003;11:506-9.)**

Key words: atrial fibrillation, left atrial appendage, occluder, thromboembolic risk

Patients with atrial fibrillation (AF) have an increased risk of thromboembolic stroke. The ischaemic stroke risk for patients with nonrheumatic AF can be predicted using clinical classification schemes.[1] Risk is increased for patients with recent congestive heart failure, hypertension, age above 75 years, diabetes and previous stroke. It is estimated that 20% of all strokes are caused by AF.[2] Oral anticoagulation significantly reduces the risk of stroke or embolism in patients with AF, but does not eliminate the risk completely.[3] However, anticoagulation is often difficult to use because it has a narrow therapeutic range, its efficacy requires regular monitoring (expressed as INR) and it is not without complications.[4,5] Sometimes it is even contraindicated. Anticoagulation is probably underused.[6,7] Approximately 90% of atrial thrombi in nonrheumatic AF are found in the left atrial appendage (LAA).[8] Occlusion or resection of the LAA therefore seems an alternative to anticoagulation in the prevention of thromboembolic events. For this reason the American College of Cardiology/American Heart Association guidelines for mitral valve surgery recommend amputation of the LAA during the operation.[9] A newly developed device allowing percutaneous LAA occlusion (PLAATO) might be an alternative to oral anticoagulation for patients with a high thromboembolic risk and contraindication to anticoagulation.

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Methods

Patients

Three patients with nonrheumatic AF and contraindications to oral anticoagulation therapy and at a high risk of thromboembolic stroke were offered this alternative therapy. The patients were all included in the ongoing prospective, multicentre, nonrandomised international PLAATO trial (principal investigator: Horst Sievert MD, Frankfurt, Germany). In this trial patients are included with continuous or paroxysmal nonrheumatic atrial fibrillation who are at risk of thromboembolic stroke, have been suboptimally controlled on oral anticoagulation or who are not a candidate for oral anticoagulation. Primary endpoint of this trial is the stroke or vascular death rate at 150 patient implant years. The institutional review board approved this study and written informed consent was obtained from all patients. Patient data and contraindications for oral anticoagulation are shown in table 1.

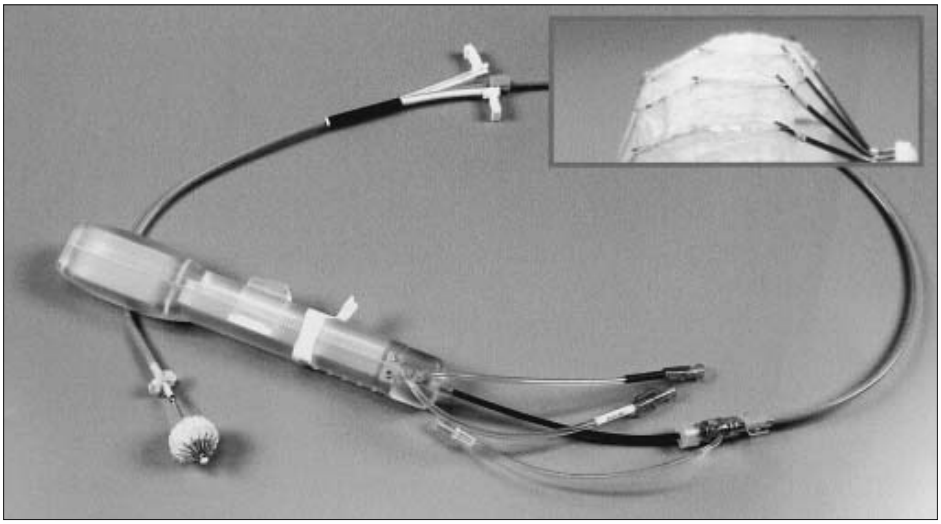

Figure 1. PLAATO device mounted on the delivery system. Inset: detailed view of the device, clearly showing the anchors along the struts.

PLAATO device

The PLAATO implant (Appriva Medical Inc, Sunnyvale, CA, US) is a self-expanding nitinol (a nickel-titanium alloy) cage covered with an occlusive membrane of expanded polytetrafluoroethylene (ePTFE) which is laminated directly to the frame structure and supported so that the perimeter has intimate contact with the inner wall of the appendage (figure 1). The implant is available with diameters of 15 to 32 mm. The purpose of the membrane is both to occlude the orifice of the LAA and to allow tissue incorporation into the device. Small anchors along the struts assist with device anchoring. The device is delivered through a 12 Fr transseptal sheath.

Table 1. Patient characteristics.

Patient number	Age (years)	Risk thromboembolic event	Contraindication anticoagulation
1	35	- Paroxysmal AF - CVA, right-sided paresis - TTE: LA 41 mm, normal LV	- Inability to maintain stable INR - Poor oral anticoagulant compliance
2	74	- Persistent AF - TTE: LA 46 mm - Hypertension - Age	- Subdural haematoma despite INR 2.5 - Frequent rectal adenoma
3	76	- Persistent AF - TTE: LA 43 mm - Age	- Ulcerative colitis

AF=atrial fibrillation, CVA=cerebral vascular accident, INR=international normalised ratio, LA=left atrium, LV=left ventricle, PAF=paroxysmal atrial fibrillation, TTE=transthoracic echocardiogram.

Procedure

Transoesophageal echocardiography (TOE) was performed immediately before the procedure to exclude clots in the LAA and to measure the size of the orifice of the LAA and its length. The procedure was performed under light sedation with diazepam if needed. Transseptal puncture was performed under intracardiac echocardiography (ICE, Boston Scientific, Natick, MA, US) guidance and fluoroscopy as described before.[10] After transseptal access, heparin was given to keep the activated clotting time (ACT) >250 seconds. Angiography was carried out to assess the size and shape of the LAA. TEE measurements and angiography were used to choose the size of the device. The device used had a diameter 20 to 40% larger than the LAA ostium diameter measured. Contrast angiography both proximal and distal to the device was used to check for proper positioning and to exclude leaks. TOE was used to assess stability and sealing. If positioning or sealing is not adequate the device can be collapsed and repositioned at this stage.

All patients were placed on acetyl salicylate acid 80 mg a day indefinitely and clopidogrel 75 mg a day for the six months following the procedure.

Follow-up

All patients will be seen regularly for up to 24 months in the outpatient clinic. The National Institutes of Health (NIH) Stroke Scale[11] will be administered at baseline and at follow-up visits to detect neurological changes attributable to embolic events. TOE will be performed at two months' follow-up and if clinically indicated.

Results

The LAA occlusion was successfully performed in all three patients. No device had to be removed and changed for a new size. The devices used had diameters of 26, 26 and 29 mm. Mean procedure time from puncture to the removal of all sheaths after the procedure was 200, 151 and 200 minutes. The procedure was well tolerated by the patients. A small amount of pericardial fluid (0.6 and 0.7 mm) was seen on transthoracic echocardiography immediately after the procedure in two patients, which was diminished the next day.

Discussion

Since in AF the majority of thrombi are located in the LAA, occlusion or resection seems a logical alternative to oral anticoagulation. Because of the preference for clot formation in this location, the LAA has been called our 'most lethal appendage'.[12] Ligation of the LAA is routinely carried out during mitral valve surgery and maze procedures in many centres. For this reason a percutaneous LAA transcatheter occlusion device was recently developed. Feasibility was proved in mongrel dogs.[13] It was found at three months that the atrial-facing surface of the occlusion membrane is completely covered with a neointimal layer. Thrombus formation on the surface of the membrane was excluded. Recently the first experiences in patients were reported.[14,15] It was concluded that transcatheter occlusion of the LAA in humans was possible and that this device may be an alternative for patients with AF not suitable for oral anticoagulation.

The LAA has long been considered an insignificant appendage. More recent research, however, found that the LAA has a role as decompression chamber when left atrial pressure is high and is an important site for the production and release of the atrial natriuretic factor (ANF).[16] Elimination of the LAA could, therefore, have important unwanted haemodynamic consequences.[17] However, echocardiographic evaluation of left atrial function in sinus rhythm after transcatheter occlusion did not show major changes in dogs.[13] The role of the LAA during atrial systole is expected to be less important in AF than during sinus rhythm. Nevertheless, careful monitoring of the trial patients in this respect is warranted. Although oral anticoagulation is successful in reducing the risk of thromboembolism, it is associated with several drawbacks that limit its use. The search for alternatives is therefore meaningful. Besides transcatheter occlusion, alternative medication should be considered. Aspirin proved to be of limited value in all the major studies. Recently the new antithrombin drug ximelagatran was reported to be promising in this respect.[18-20] The role of ximelagatran in patients with contraindications to oral anticoagulation needs to be defined.

Conclusions and limitations

Transcatheter occlusion of the LAA is feasible. It is not considered suitable for the majority of AF patients due to its invasive character. In the small number of patients treated so far, the perspective of such therapy is promising. Long-term follow-up with respect to efficacy and haemodynamic side effects is lacking. Its future role in prevention of thromboembolic events needs to be defined. Furthermore, the combined use of aspirin and clopidogrel after implantation is equally contraindicated in a subset of patients with increased risk of bleeding. In a large group of patients with AF, new antithrombin drugs are probably a more acceptable alternative to the currently used vitamin-K antagonists. ■

Note

For physicians interested in further information, or in patient referral, please see our website www.thoraxcenter.nl.

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Chapter 6

Anticoagulation in atrial fibrillation and flutter, a review

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Europace 2005;7:492-499

Anticoagulation in atrial fibrillation and flutter

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Submitted 8 October 2004, and accepted after revision 5 May 2005
Available online 25 July 2005

KEYWORDS
atrial fibrillation;
anticoagulation;
catheterablation

Abstract Atrial fibrillation and atrial flutter are important risk factors for stroke. Based on a literature search, pathogenesis of thromboembolism, risk assessment in patients, efficacy of anticoagulation therapy and its alternatives are discussed. Special emphasis is put on issues like paroxysmal atrial fibrillation, atrial flutter and anticoagulation surrounding catheter ablation and cardioversion. A strategy for anticoagulation around the time of pulmonary vein ablation is suggested.

Introduction

Atrial fibrillation (AF) is an important public health problem affecting approximately 1% of the general population. As the frequency of AF increases with age, it is anticipated that the number of people with AF will double in the next 25 years [1]. One of the major goals in treating AF is a reduction in the incidence of thromboembolic stroke, the most feared complication of AF. It is estimated that about 17% of all strokes are caused by AF [2]. Ischaemic stroke associated with AF is nearly twice as likely to be fatal as non-AF stroke and the functional deficits among survivors more severe [2,3]. In the Framingham Study the risk of stroke in patients with non-valvular AF was increased five-fold in comparison with the general population [4]. Valvular AF increases this risk to 17-fold [5].

Atrial fibrillation and thromboembolism: pathogenesis and risk assessment

The loss of coordinated atrial contraction is important for thrombus formation in patients with AF [6].

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1099-5129/$30
doi:10.1016/j.eupc.2005.05.012

Patients with atrial flutter (AFL) and impaired left atrial appendage (LAA) function are also potentially at high risk for thromboembolism and might therefore require anticoagulation [7]. Approximately 90% of atrial thrombi in non-rheumatic AF are found in the LAA [8]. Patients less than 60 years of age, without cardiovascular disease, however, have a low risk of stroke. Other factors, such as age and associated cardiovascular disease play a greater role. Platelet activation, on the other hand, probably does not play a significant role in thrombus formation in these patients [9]. Five large, randomised trials of anticoagulation were pooled by The Atrial Fibrillation Investigators [10] and risk factors for stroke were defined. Age was shown to increase stroke risk by 1.4 per decade. Other risk factors include previous stroke or transient ischaemic attack (TIA), hypertension, diabetes mellitus, congestive heart failure, ischaemic or rheumatic heart disease, prior thrombo-embolism and female gender (Fig. 1). Patients with rheumatic heart disease, prosthetic heart valves, prior thromboembolism and persistent atrial thrombus detected by transoesophageal echocardiography (TOE) are considered to be at highest risk [11,12]. Risk stratification using schemes such as the $CHADS_2$ algorithm can help to quantify the stroke risk for patients with AF [13] (Table 1). $CHADS_2$ is a risk assessment algorithm derived from pooled data. Consistent with ACC/AHA/ESC guidelines [11] for patients with AF and additional risk factors, any patient with a $CHADS_2$ score ≥ 1 should be considered for long-term anticoagulation.

Transoesophageal echocardiography (TOE) is superior to transthoracic echocardiography both in assessment of left atrial, and left atrial appendage thrombus, as well as in detection of reduced flow velocities and spontaneous echo contrast in the left atrium and left atrial appendage [14]. TOE is also the method to detect a patent foramen ovale (PFO), a known cause of paradoxical emboli causing stroke or transient ischaemic attacks [15]. An association of PFO and septal aneurysms with stroke exists; a relation with AF is not described. Patients with AF and complex atherosclerotic plaques in the aorta have a substantially higher risk for stroke [16,17].

Table 1 The $CHADS_2$ algorithm [1,3]

	$CHADS_2$ risk factors	Points
C	Recent clinical congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75 years	1
D	Diabetes mellitus (any form)	1
S	History of stroke or transient ischaemic attack	2

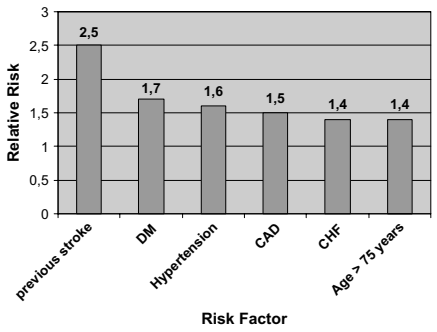

Figure 1 Relative risk compared with those with AF, but without these risks. CAD: coronary artery disease, CHF: congestive cardiac failure, DM: diabetes mellitus, TIA: transient ischaemic attack. *Adapted from reference [11].

Efficacy of anticoagulation

Pooled data analysis for oral anticoagulation with coumadins has shown a relative risk-reduction for stroke of between 62 and 70% [10,18]. The risk reductions for stroke were 2.7% per year for patients without a history of stroke or transient ischaemic attack, and 8.4% per year for secondary prevention in patients with a prior stroke [12,19]. Recently, it was established that anticoagulants should be withheld during the first 14 days in AF patients with acute ischaemic stroke as the benefit was completely negated by a higher risk of intracranial bleeding [2].

Level of anticoagulation

Oral anticoagulation has a narrow therapeutic window. When the international normalized ratio (INR) is above 2.0 the risk of ischaemic stroke is low [20]. Above the level of 4.0, however, the risk of haemorrhagic complications, especially intracranial bleeding, increases significantly [21—23]. For those who continue to have TIAs or strokes despite a therapeutic INR or those who have a mechanical heart valve, many experts recommend a target INR of 2.5 to 3.5 [24]. Risk factors for major bleeding includes an INR ≥ 4.0, advanced

age, a history of stroke and hypertension [25,26] and unstable INR control [21]. A cohort study identified three risk factors for haemorrhage in an elderly population: alcohol abuse, chronic renal insufficiency and previous gastrointestinal bleeding [27].

Alternatives to standard oral anticoagulation

Aspirin alone or in combination with low dose warfarin [28] has been studied. The combination of aspirin with low dose warfarin does not improve the risk/benefit ratio [29]. Aspirin alone has a modest benefit. A meta analysis calculated a risk reduction of only 21% [30]. The new anti-thrombin drug ximelagatran has been reported to be a promising alternative to warfarin [31]. It has been shown to be equally effective, or at least not inferior to well controlled warfarin [32]. Further, it has the advantages of less drug interactions, an almost immediate anticoagulant action, the absence of the need for regular dose adjustments and a lower bleeding risk. However, drug-related liver injury, led the United States Food and Drug Administration not to approve its use [32,33].

Fondaparinux and idraparinux are investigational agents that prevent thrombin formation [34—37]. They are parenteral, specific, indirect, factor Xa inhibitors with a mechanism of action similar to that of heparin.

Because 90% of atrial thrombi in non-rheumatic AF are found in the left atrial appendage (LAA) [8], occlusion or resection of the LAA seems an alternative to anti-coagulation in the prevention of thromboembolic events in some patients. A newly developed device allowing percutaneous LAA occlusion (PLAATO) might be an alternative to oral anticoagulation for patients with a high thromboembolic risk and a contraindication to anticoagulation [38], and its value is currently being assessed.

Usage of anticoagulation

Several reports indicate that anticoagulation is actually underused in AF patients at high risk for thromboembolic complications [39,40]. Possible explanations for this underuse are doubts about the effectiveness of anticoagulation, the fear of haemorrhagic complications such as intracerebral bleeding and the limitations of its use, such as frequent coagulation monitoring and interactions with food, alcohol and other drugs. Patient self-testing and self-management has been shown to improve the accuracy and quality of oral anticoagulation [41,42] and may improve quality of life.

Special issues

Paroxysmal and persistent AF

In the trials of anticoagulation in AF, between 5 and 25% of the patients had what was labelled at that time paroxysmal or intermittent AF. In this group the same risk reduction for stroke was found as in patients with permanent AF. Patients with paroxysmal AF and with risk factors for stroke should therefore be treated with anticoagulation [43]. The AFFIRM [44] and RACE trials [45] both compared the benefits of rate in AF control versus rhythm control (sinus rhythm). In these two studies, most patients who experienced an ischaemic stroke either had a suboptimal INR or had discontinued anticoagulation. A very important observation was that 75% of the patients with an ischaemic stroke in the rhythm-control group in the AFFIRM trial were believed to be in sinus rhythm at the time of the event. Both trials give reason to reconsider the cessation of anticoagulation after a successful cardioversion in patients with stroke risk factors [46].

Atrial flutter

In recent literature, controversy exists about the need for anticoagulation surrounding cardioversion of lone atrial flutter [47,48]. The acute and chronic haemodynamic effects of flutter are not completely understood. After cardioversion of flutter, the atria remain stunned for up to 2 weeks, as has also been shown for AF [49]. The reported incidence of LAA thrombi in patients with lone atrial flutter varies from 1% [47] to 11% [50]. The prevalence of LAA thrombi also increases with age and with lower ejection fraction [51]. Lone atrial flutter has a similar stroke risk to lone atrial fibrillation, presumably because it carries a risk for subsequent development of atrial fibrillation that is higher than the general population. Furthermore, atrial flutter maybe the result of drug treatment of AF. In an unselected patient group with atrial flutter, Seidl et al. [52] found a remarkably high overall embolic rate of 7%. In this group the majority of patients were not receiving oral anticoagulation. Hypertension appeared to be the only independent risk factor. In patients with

atrial flutter, markers of a prothrombotic state (d-dimers and β-thromboglobulin) are not elevated, except for those patients with impaired LAA function as assessed by TOE. Anticoagulation should be considered for all patients with atrial flutter who are older than 65 years of age [53] and is mandatory in the period before and after electrical cardioversion [50,54,55].

In conclusion, anticoagulation in atrial flutter patients should use the same approach as in patients with atrial fibrillation [56,57].

Anticoagulation and prophylaxis of thromboembolism in radiofrequency (RF) ablation of atrial fibrillation and flutter

The treatment of AF entered a new era after the publication of the landmark observations of Haïssaguerre et al. [58]. The recognition of the role of the myocardial sleeves [59] within the pulmonary veins (PVs) in initiating AF changed both pathophysiological insights and therapeutic approaches. Segmental ostial catheter ablation [60] and left atrial encircling ablation of the PVs [61] have both been reported to be successful in the treatment of AF. RF ablation is a highly effective therapeutic approach in the treatment of typical isthmus dependent atrial flutter [62].

RF catheter ablation is complicated by thromboembolism in about 0.6% of patients [63]. The risk of stroke from RF ablation may be higher in paroxysmal AF patients with prior transient ischaemic attack [64]. As reflected by elevated plasma d-dimer levels, RF ablation has a thrombogenic effect that persists through the first 48 hours after the procedure [65]. Activation of the coagulation cascade in RF ablation procedures is not related to the delivery of RF energy, but is related to the placement of intravascular catheters and to the duration of the ablation procedure [66,67]. Furthermore, RF lesions themselves have been shown to be thrombogenic in acute studies [68]. The risk of a thromboembolic complication is higher for left sided ablations (1.8%—2.0%) [63]. By administering intravenous heparin immediately after introduction of the venous sheaths, haemostatic activation is significantly decreased [69]. There is also a significant risk for thromboembolism in patients referred for ablation of typical atrial flutter who have not been appropriately anticoagulated [70]. Radiofrequency ablation of chronic atrial flutter is associated with significant left atrial stunning [71].

The NASPE Policy Statement on Catheter Ablation [72] suggests anticoagulation for at least 3 weeks prior to ablation for AF and atrial flutter for patients who are in these arrhythmias. Discontinuation of anticoagulants 2 to 3 days before the procedure is possible. For high-risk patients, heparin to cover this period should be considered [72]. TOE shortly before pulmonary vein ablation to exclude left atrial thrombi is routine in many clinics [73,74]. We observed an atrial thrombus on TOE in 9% of patients referred to us for PV isolation (in press). Generally during left sided ablation, heparin should be administered, aiming at an activated clotting time (ACT) of 250—300 seconds. Higher levels of anticoagulation (ACT $\geq$ 300 seconds) are used for pulmonary vein ablations [72]. No clear guideline appears to exist regarding the use of anticoagulation after a successful pulmonary vein isolation procedure. However, it seems logical to continue oral anticoagulation for some time after the procedure. The duration will depend on pre-existing risk factors. Experienced groups continue anticoagulation therapy at least 3 months after a successful ablation [73,75,76].

Anticoagulation surrounding cardioversion for atrial tachyarrhythmias

Thromboembolic events after cardioversion in atrial tachyarrhythmias have been reported in 1% to 7% of patients not receiving prophylactic anticoagulation [77,78]. Anticoagulation is recommended for 3 to 4 weeks before and after cardioversion for patients with AF of unknown duration and for AF of more than 48 hours duration [11]. A reasonable alternative strategy is early cardioversion with a short period of anticoagulation therapy after exclusion of LA/LAA thrombi with TOE [79].

Anticoagulation in the elderly

Anticoagulation in those over 75 years of age has been poorly assessed, as this age group was not well represented in the majority of clinical trials of anticoagulation. Clearly, age increases the risk of complications of anticoagulation, but conversely these patients are also at the highest risk of stroke [80], so risk assessment and therapy should be individualised [81].

AF in association with valve prostheses

In patients with bioprosthetic valves and AF, similar levels of anticoagulation to those mentioned above seem adequate. In AF associated with mechanical valve prostheses, levels of anticoagulation recommended are less standardised,

Table 2 ACC/AHA/ESC atrial fibrillation guidelines-anticoagulation

Patient features	Antithrombotic therapy	Grade of recommendation
Age <60 years No heart disease (lone AF)	Aspirin (325 mg per day) or no therapy	1
Age <60 years Heart disease but no risk factors*	Aspirin (325 mg per day)	1
Age ≥60 years No risk factors*	Aspirin (325 mg per day)	1
Age ≥60 years With DM or CAD	Oral anticoagulation (INR 2.0—3.0) Addition of aspirin daily optional	12b
Age ≥75 years, especially women	Oral anticoagulation (INR approx 2.0)	1
Heart failure EF <0.35 Hypertension Thyrotoxicosis	Oral anticoagulation (INR 2.0—3.0)	1
Rheumatic heart disease Prosthetic heart valve Prior thromboembolism Persistent atrial thrombus on TOE	Oral anticoagulation (INR 2.5—3.5 or higher may be appropriate)	1

* Risk factors for thrombo-embolism include HF, LV EF <35% and history of hypertension. AF: atrial fibrillation, CAD: coronary artery disease, DM: diabetes mellitus, EF: ejection fraction, INR: international normalised ratio, LV: left ventricle, TOE: transoesophageal echocardiography. Adapted from reference [11].

but what is clear is that the risks for thromboembolism depend on the type of valve inserted and its position [82,83]. Accordingly, the target INR for these patients should be individualised and the presence or absence of AF has little influence on this target.

Conclusions

The evidence strongly supports the use of oral anticoagulation, aiming at an international normalised ratio (INR) between 2 and 3, in patients with AF who have an average or higher risk of stroke. This also includes the elderly. Only in younger patients without additional risk factors is the use of oral anticoagulation not indicated. Aspirin is advised by the guidelines (Table 2) for lower risk patients [11] but a true evaluation in this patient group is lacking [84]. Paroxysmal AF and atrial flutter should be treated in the same way as persistent and permanent forms of AF. For high-risk patients with a contraindication to anticoagulants, a left atrial occluder may be valuable, and is currently under investigation. Guidelines for the use of anticoagulation surrounding pulmonary vein isolation are not yet available, but a high level of anticoagulation is necessary during the procedure. It is appropriate to prescribe oral anticoagulation before and to re-initiate it after the procedure. A covering period with heparin until the INR reaches the level of 2 is advisable. It is possible that medical practice will change with the introduction of new antithrombin drugs and with further documentation of the efficacy of low molecular heparin in this area. The initial optimism over the introduction of ximelagatran has been tempered by criticism on the basis of its side effects [33].

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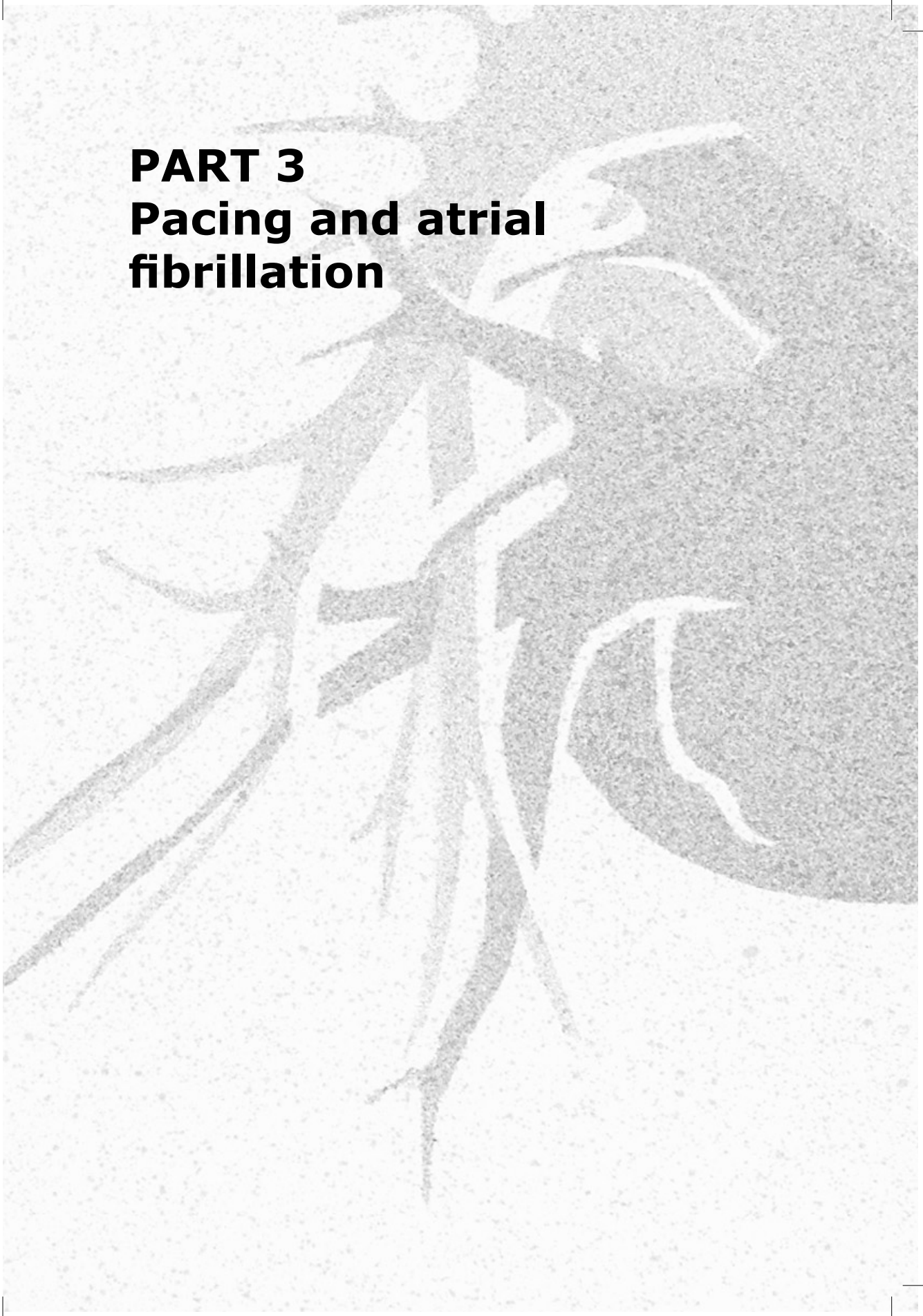

PART 3
Pacing and atrial fibrillation

Chapter 7

The ultimate device in the treatment of atrial fibrillation

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Bookchapter; Einthoven 2002, 100 years of Electrocardiography
Ed: Martin J. Schalij et al.ISBN 90-9015912-6 p 409-413

THE ULTIMATE DEVICE IN THE TREATMENT OF ATRIAL FIBRILLATION

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Atrial Fibrillation (AF) is the most frequently encountered arrhythmia. The disease is multifactorial, with a complex epidemiology, a changing appearance in time and symptoms. It leads to short and long term symptoms. AF may considerably impair quality of life. On the long run, cardiac function can deteriorate and it is associated with thromboembolic complications including cerebral stroke.

Therapy is complex and a highly variable response to therapeutic attempts can be expected. Apart from being not very effective, antiarrhythmic drugs have many shortcomings and side effects. Non-pharmacological, interventional techniques are therefore often justified.

The different appearances of AF

This complex arrhythmia may present itself in different ways. Attempts to classify the disease have been made over the last years [1], but finally it becomes accepted that acute manifestations are different from chronic forms, which can be divided in paroxysmal (i.e. intermittent, usually self terminating), persistent (which requires an intervention), and permanent (when the condition remains present)[2]. These classifications do not deal with different aetiologies and mechanisms, which can all lead

a similar electrocardiography pattern. Underlying differences in pathophysiology, and disease stage or severity can lead to a different outcome after interventions with drugs, ablation and devices.

Device therapy

Device therapy certainly plays a role in the treatment of AF, from the time on that pacemakers were introduced for atrial bradyarrhythmias. The role in isolated atrial tachyarrhythmias is less clear, but was the subject of recent investigations. These made it clear that devices can play a role as monitor, but also as tools to prevent and terminate AF in certain conditions in a limited patient group. AF initiates processes of remodelling within the atrial myocardium and has the tendency to perpetuate itself [3]. Therefore, prevention or termination of AF episodes immediately after onset theoretically is desirable to prevent or to delay the progression of the disease. This reduces the option of an `ultimate` device to a device, which can convert AF with shocks or other means. Implantable device therapy is a field of rapid clinical progress and technologic advances. Conventional atrial pacing has undergone several randomised studies, and seems to be disappointing. New, preventive pacing algorithms are promising in some conditions, and anti tachycardia pacing is now incorporated in implantable devices. Experimental burst pacing was recently tested for the first time on a chronic basis.

The implantable device as a monitor

Old fashioned pacemakers use rate criteria, including rate regularity or mode switches to suggest that AF is present. The improved memory capabilities of modern devices add an important diagnostic tool in the treatment of cardiac arrhythmias. Marker channels and electrograms are now important sources of information. The medical community learned a lot about the natural course of AF in trials and registries with implanted devices[4, 5 6]. More recent AF trials demonstrated that the conventional diagnostics still have serious limitations. It is not unthinkable that a device is used just to monitor the disease, and its reaction to drug therapy, as could be done with an implantable ECG loop recorder [7]. Further, haemodynamic measurements by devices are no longer a dream and it is even possible to understand the (anti-)coagulation status of a patient using the appropriate sensors. Additionally, it is conceivable that patients can be monitored at home with an implanted device, through the internet or a satellite.

The rationale for preventive conventional atrial pacing

The idea of pacing for the prevention of AF was stimulated by the successful use of atrial pacing in the sick sinus syndrome[8, 9] and of post operative overdrive pacing af-

ter coronary artery bypass grafting[10]. Atrial Fibrillation is a re-entrant rhythm, often induced by triggers such as atrial premature depolarisations (APD) in the presence of a substrate like intra-atrial conduction abnormalities and increased dispersion of refractoriness[11]. Areas within the atria with a longer refractory period are the first to cause conduction delay or block in case of an APD. Atrial pacing may reduce bradycardia-induced dispersion of atrial repolarisation. APD's can be successfully suppressed by atrial overdrive stimulation[12, 13].

The rationale for sophisticated preventive atrial pacing

Dedicated pacing algorithms have been designed to provide almost permanent atrial overdrive, to prevent post extrasystolic compensatory pauses (prevention of pro-arrhythmic short-long-short cycles) and to provide post mode-switch overdrive pacing because the atria are more vulnerable for recurrence after a period of atrial fibrillation (electrical remodelling).

The rationale of alternative pacing sites

During extrastimulus testing intra-atrial conduction delay and dispersion of refractoriness are site dependent. This probably reflects the possible effects of atrial extrasystoles in real life. Pacing the high right atrium (HRA) from the appendage or free wall is often the source of delayed intra-atrial conduction and disco-ordinated left and right atrial mechanical function [14]. Patients with AF induction during HRA stimulation also manifest non uniform anisotropic conduction in the triangle of Koch. Distal coronary sinus (CS) pacing pre-excites this critical area for re-entry, thus prohibiting AF induction by APD's from the HRA [15]. Multisite pacing (i.e. pacing the HRA and CS os region simultaneously) reduces the ability to initiate AF with APD's by reducing the window for AF induction and minimising the dispersion of atrial refractoriness[16]. Septal pacing is associated with a decreased atrial activation time (paced P-wave duration) and is associated with a reduced progression to chronic AF [17, 18].

Clinical value of preventive pacing

Pacing for the prevention of AF using standard lead positions is currently only well proven in patients with the sick sinus syndrome[8, 9]. For AF in the non-bradycardia patient, conventional pacing seems to be not effective at all [19]. The above mentioned algorithms were studied in two non published trials (the ADOPT-A study and the AF Therapy trial) . They showed conflicting results, possibly partly due to differences in patient selection and endpoints. Interestingly, Friedman et al showed a trend toward a reduction in the number of AT/AF episodes per month (the `AF burden`) in the Jewel AF study[6]. Clearly, more studies are necessary to establish the real value

of these algorithms (and endpoints). Given the positive effects of placing the atrial lead in the septum instead of the traditional right atrial appendage this probably should be considered.

Device Therapy to terminate AF (Cardioversion)

A very high success rate in cardioversion was achieved by the implantable cardioverter[4]. The safety and efficacy was demonstrated [4] in a huge number of episodes. The Metrix atrial defibrillator (InControl Inc, Redmond, WA, USA) uses 2 detection algorithms which run in series. The result of both algorithms is a high sensitivity (92%) and specificity (96%) for the detection of AF[4]. Its real limitation was that this system was only studied in lone AF, without pacing modalities. Doubts exist whether the atrioverter efficacy data can be extrapolated to sicker patients. Nevertheless, in an ambulatory setting, most patients were satisfied, and only a single shock was required [20].

A first problem is the shock configuration. One has to be sure that both atria are covered by the defibrillating field. It seems that with most investigated configurations, shocks will fail from time to time. It has to be noted that standard ICD's with an active pectoral can and a ventricular coil seem to be effective for cardioversion of AF using low energy shocks ($\leq$ 3J) in 57%[21]. This has consequences for conventional ICD`s, and for patients who suffer from AF in the course of another treatment.

Secondly, the pain caused by the cardioverter shock limits its clinical use, and is another problem. Discomfort is related to the number of shocks, more than to the energy level [22]. One of the determinants of pain during shock delivery could be the waveform of the shock. It is not impossible that pain perception increases with higher voltages as required with a lower capacitance [23]. This was also observed in more recent studies comparing active can defibrillation and defibrillation with double intracardiac coils [24].

The third limitation is the remote fear for pro-arrhythmia (which was completely absent in the InControl trial), necessitating ventricular backup shocks. This is circumvented by current ICD's, which can recognise atrial, ventricular and double tachycardias. This paves the way to make every ICD suited for full AF treatment.

Concomitant atrial arrhythmias

AF is often associated with other atrial arrhythmias (flutter, ectopic tachycardia). These can be terminated by other means than a shock[25]. Termination of `organised` forms of AF can be achieved by very rapid atrial pacing (50 Hz pacing)[26] with modest efficacy. Devices that terminate atrial arrhythmias require specific sensing and detection capabilities. The device must sense low and varying amplitude atrial electrograms during AF. This should be discriminated from all these other arrhythmias.

Hybrid techniques for all?

We tend to go for device therapy when other invasive techniques have failed. This will include flutter ablation, and for some patients ablation of the AV Node or other ablative techniques in the right or left atrium. Some suggest that only 30% will have improvement after focal ablation[27]. This suggests that a large group of patients might benefit from combining ablation with an ultimate device.

Conclusion

In the treatment of AF there is a role for devices. The ultimate device should be a perfect monitor, should have atrial and ventricular sensing modalities. For atrial pacing, septal or multisite approaches must be considered. Devices with preventive pacing algorithms without the possibility to cardiovert AF should not be implanted routinely because the results of the mentioned algorithms so far are very poor. A reliable discrimination between atrial tachycardia and atrial fibrillation is mandatory. Only then atrial ATP can be incorporated. The hypothesis that sinus rhythm begets sinus rhythm remains attractive because of the follow-up we have now[3]. However, the hypothesis is far from being proven. That defibrillators will play an important part in the management from subsets of patients with atrial fibrillation is without any doubt. The combination of all these tools will certainly be an asset.

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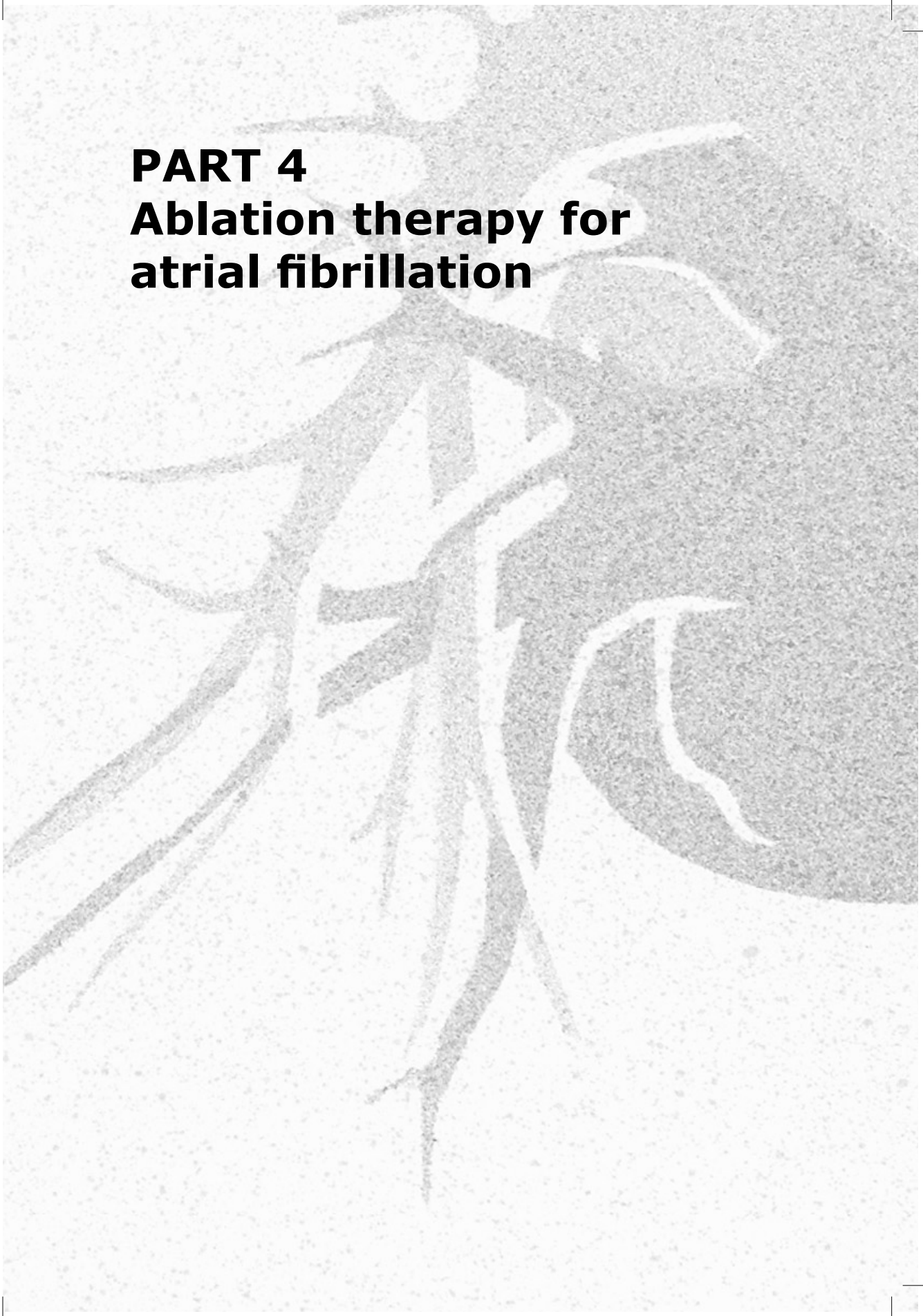
PART 4
Ablation therapy for atrial fibrillation



Chapter 8

Targets and endpoints of ablation therapy for atrial fibrillation in light of pathophysiologic mechanisms

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in press: The Journal of Interventional Cardiac Electrophysiology

TARGETS AND ENDPOINTS IN ABLATION THERAPY FOR ATRIAL FIBRILLATION IN LIGHT OF PATHOPHYSIOLOGIC MECHANISMS

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Abstract:
Atrial fibrillation (AF) is a complex and multifactorial arrhythmia. AF is an important public health problem. Non-pharmacological AF treatment for symptomatic patients is of increasing importance. The different catheter ablation techniques in AF treatment developed during the recent years, all based on different pathophysiological insights, are discussed. Several methods for follow-up after ablation are used and make comparison of results difficult.

Key Words. Atrial fibrillation, mechanisms, catheter ablation, follow-up

1. Introduction

Atrial fibrillation (AF) is an electrocardiographic description of a complex and multifactorial arrhythmia. Excellent overviews of early descriptions and proposed mechanisms of AF can be found elsewhere [1-3]. Chronic AF is classified into paroxysmal, persistent and permanent forms [4]. Paroxysmal AF refers to short lasting episodes that stop spontaneously. Persistent AF needs cardioversion to convert to sinus rhythm. In the case of the permanent form, AF cannot be cardioverted or is accepted. Three randomized trials [5-7] failed to show a reduction in stroke or mortality with a primary strategy of pharmacological rhythm control compared with a strategy of rate control while accepting AF. This is probably due to the severe side effects of anti-arrhythmic drugs and stresses the importance of research in the field of non-pharmacological AF treatment for symptomatic patients.

2. Epidemiology of Atrial Fibrillation

AF is an important public health problem affecting approximately 1% of the general population. The prevalence of atrial fibrillation is approximately 10% in persons older than 70 years [8] and rises to 17% in those aged 84 years or more [9]. As the incidence of AF increases with age, it is anticipated that the number of people with AF will double in the next 25 years [10]. AF is a cause of significant morbidity and mortality. AF is an independent risk factor for stroke [11]. The risk for stroke is further increased in patients with AF because of concomitant risk factors for stroke such as advanced age, hypertension, coronary heart disease and heart failure. AF is associated with a mortality rate twice that of age-matched controls [8] partly because of the increased incidence of stroke [12] and partly because of its association with hypertension, coronary heart disease and heart failure. Men have a 50% higher risk of developing AF [13,14]. The absolute number of men and women with AF is however equal, and after age 75 years, 60% of the people with AF are women, because women live longer [15].

3. Catheter ablation of atrial fibrillation and its endpoints in light of pathophysiologic mechanisms

We have summarized the actual approaches with their rationale in table 1.

3a AF as a re-entrant arrhythmia

It was originally thought that AF was the result of multifocal atrial activity [1]. Moe hypothesized and described the propagation of multiple wavelets in the atria [16]. This was later supported by mapping studies [17]. The most important element of this model is the heterogeneous distribution of atrial refractory periods. The pathways of the wavelets are the result of these differences in local refractoriness.

Wavelets can collide, divide, disappear and meander. The reentry circuits in AF are functionally determined, in contrast to the anatomically determined reentry circuit of atrial flutter. The more wavelets that coexist together the less the likelihood of their simultaneous extinction becomes. The wavelength of a wavelet is determined by the refractory period and the conduction velocity. If the conduction velocity is decreased or the atria enlarged the chance that multiple wavelet reentry can be sustained is greater. Induced and spontaneous AF mostly terminates within minutes; therefore a substrate is required for the perpetuation of AF. Therapies that decrease the atrial dimensions or increase the wavelength (drugs that increase the conduction velocity or the refractory period) will decrease the chances of initiation or perpetuation of AF. Atrial fibrillation itself contributes to its own perpetuation by means of electrical remodelling [18]. Electrical remodelling is the shortening of the atrial refractory period and flattening of the physiological rate adaptation. Structural remodelling, which occurs after electrical remodelling [19,20] further promotes the persistence of AF.

Based on the concept that AF can only be perpetuated if 3-6 wavelets co-exist, Cox developed the maze procedure [21]. Stimulated by the success of this procedure, initial ablation attempts were made to copy the maze procedure. The idea was to segment both atria by making long linear lesions. These procedures, however, were not successful because of technical difficulties in creating continuous linear lesions, the morbidity associated with this approach, the long duration of the procedure and the moderate effect on AF burden [22].

Areas with complex fractionated atrial electrocardiograms (CFAE's) identify areas of substrate such as areas of slow conduction or the areas where the wavelets turn around arcs of functional block [23]. Nademanee et al., introduced the elimination of CFAE's as an alternative technique in the field of AF catheter ablation [24]. This approach therefore aims at changing or elimination of the substrate of AF. Endpoints used were elimination of the CFAE's, termination of AF during ablation and non-inducibility after ablation. Limitations of the technique described by Nademanee are the extensive ablation required and the relatively high number (5%) of serious complications. Another attempt to change the substrate of AF was done by Pachon et al. [25]. In a small group of patients they used fast Fourrier analysis of the endocardial left atrial signal, during sinus rhythm, to identify areas of fibrillatory conduction. These areas were ablated. In 94% of patients there was freedom of AF after a mean follow-up of 9 months with or without drugs.

3b. Role of the pulmonary veins as triggers for AF

Attention was drawn back to focal activity after publication by Haissaguerre et al. of their landmark study on the role of the pulmonary veins (PV's) in triggering AF [26]. Later it became clear that rapid firing foci could probably maintain AF as well [27]. Stable microreentrant circuits within the PV's, acting as drivers [28], together with fibrillatory conduction (spatial dissociation of fibrillatory waves caused by distribution of refractory periods) can lead to the perpetuation of AF [29,30]. The mechanism of focal firing within the myocardial sleeves around the PV's is unknown. Both micro-reentry and triggered activity have been suggested. Jais et al.[31], found different electrophysiological properties favourable for micro-reentry in PV's of AF patients (shorter effective refractory periods and long conduction times) compared with PV's of patients without AF. Continuation of firing within an isolated vein is rare. A possible explanation is that triggered activity does not occur without activation from the left atrium [32]. An increased left atrial pressure can also cause depolarisations within the PV's [33].

Originally Haissaquerre et al., performed RF ablation only at sites within the PV's where ectopic activity was recorded [26]. It is now accepted that the results of PV isolation improve if all PV's are electrically completely isolated from the left atrium.

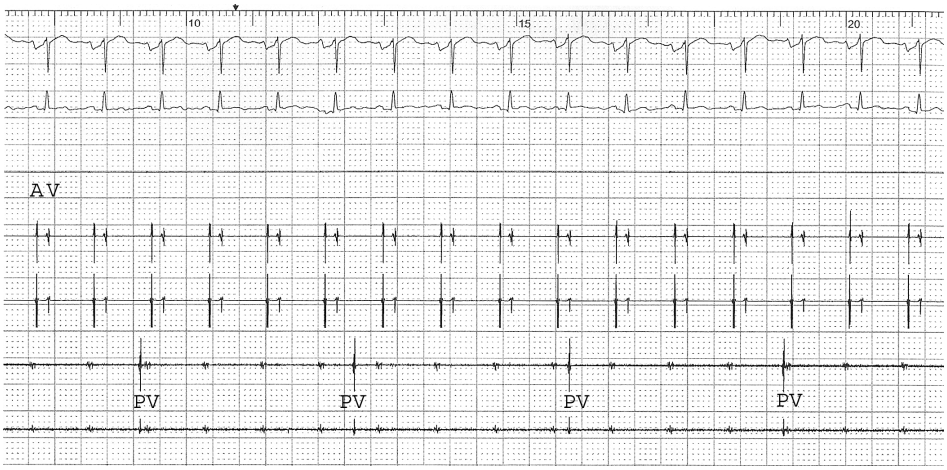

Figure 1. Dissociation of pulmonary vein activity form atrium and ventricle after ablation at the left upper pulmonary vein. A: atrium, V: ventricle, PV: pulmonary vein potential.

The endpoint of PV isolation is the elimination of all ostial PV potentials and the demonstration of complete entrance block (figure 1). Because of the risk of PV stenosis with RF energy ablation was targeted at the ostium of the PV's and other techniques, such as cryothermal ablation [34] were studied. In the intracadiac echo-

guided antrum isolation, RF ablation is done remote from the PV ostia [35]. PV isolation is the endpoint in this approach as well. The high success rate in patients with paroxysmal and persistent AF (only 12 % recurrences after a mean follow-up time of 417 ±145 days) is possible partly due to modification of the atrial substrate.

3c. The role of the autonomic nervous sytem

An alternative explanation is that firing within the PV results from triggering by ganglionic plexuses surrounding the PV's [36]. Sympathetic nerve stimulation can lead to the induction of early atrial depolarisations and therefore mainly modifies the triggers of AF. Sympathetic stimulation causes only a minor decrease in the atrial effective refractory period (AERP). Parasympathetic nerve stimulation, on the other hand, causes a large AERP decrease and an increase of AERP heterogeneity. Therefore it causes mainly a substrate modification. In this way AF can be considered to be a dysautonomia; this could be an explanation for the perpetuation of AF in structurally normal hearts. Coumel already described the concept of vagal AF in 1983 [37]. Localisation of the autonomic ganglia in the epicardial fat pads is possible by evoking a vagal response (sudden prolongation of the RR interval) by rapid pacing around the PV's and at the posterior wall of the left atrium (CL 50 msec, pulsewidth 1-10 msec, 0,5-12 V). After ablation of these ganglia this vagal response should be noninducible [36]. This concept perhaps constitutes a new approach in AF ablation (figure 2).

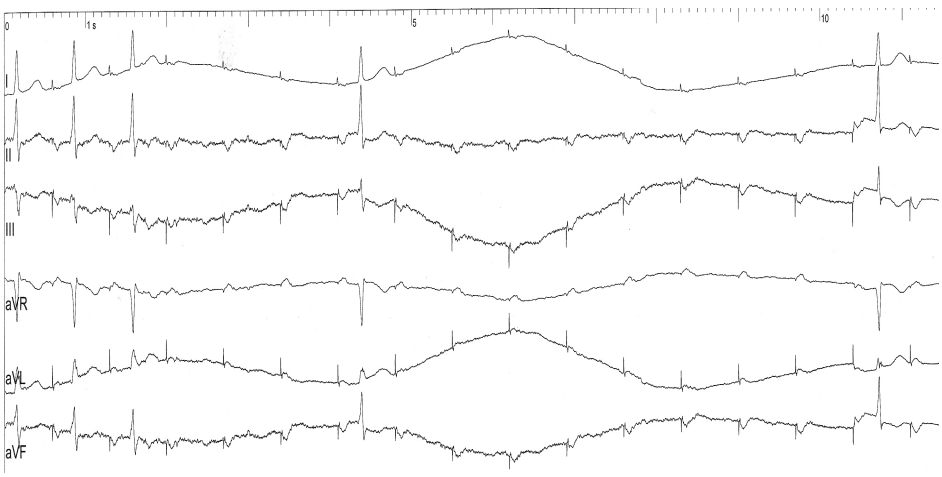

Figure 2. Bradycardia with AV block and a pause of 8 seconds during atrial pacing while ablating at the left upper pulmonary vein, remote of all conduction tissue. No pain was reported by the patient at this moment.

Ablation of the parasympathetic ganglia also contributes positively to the results of the circumferential pulmonary vein ablation developed by Pappone et al. [38]. In this technique, also known as LACA (left atrial radiofrequency circumferential ablation) continuous circular lesions (CCLs) are made around each PV or around ipsilateral PVs. This technique was originally designed to isolate the PVs with reduction of the risk of PV stenosis [39]. The ostium of the PV is identified by fluoroscopy and during withdrawal of the catheter from the PV, with a simultaneous impedance decrease and appearance of atrial potentials. RF applications are given until the local voltage decreases > 80% [39]. The endpoint is a low peak-to-peak bipolar potential (<0,1 mV) inside the circular lesion, determined by local electrographic analysis and voltage maps (figure 3).

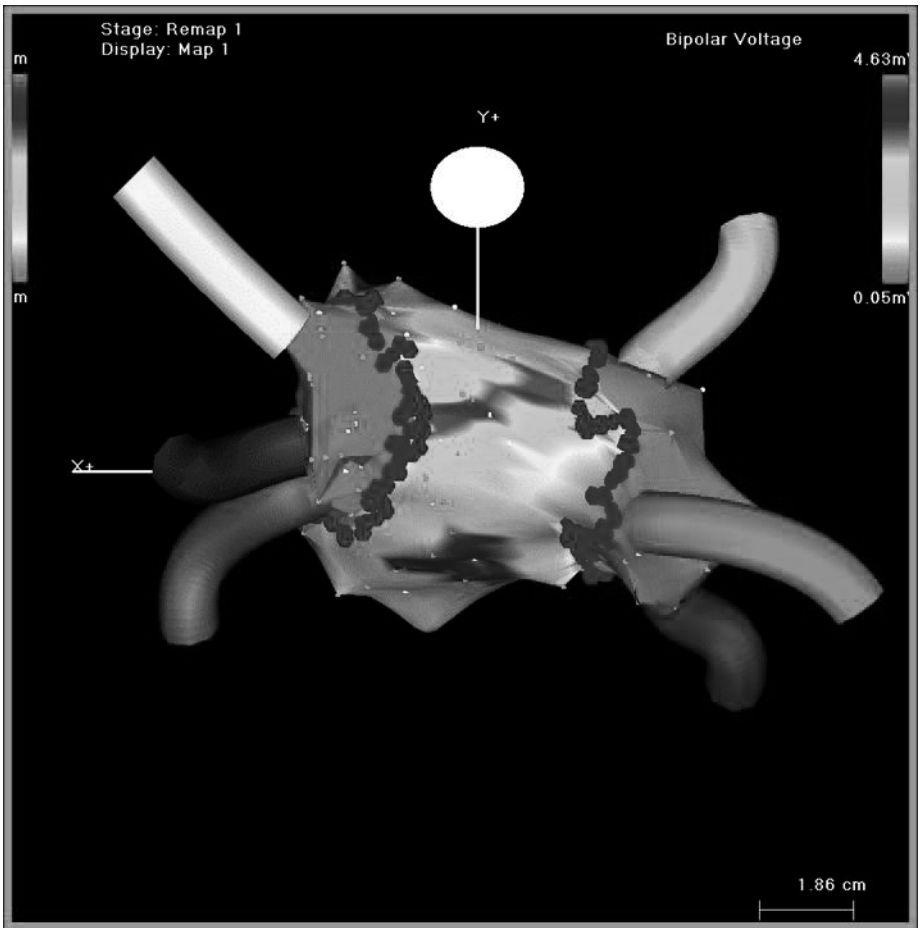

Figure 3. CARTO image after circumferential ablation. The red areas, surrounded by ablation points, encircles the right sided and left sided veins and has a voltage less than 0.50 mV after ablation

Later it was suggested that complete PV isolation is not necessary for curing AF using this approach [40]. However, Ouyang et al.[41], demonstrated that in patients with recurrent atrial tachycardias after CLL around ipsilateral PV's, recovered PV conduction was the dominant mechanism. In 7 volunteers without atrial tachycardias after CLL persistent complete isolation was found. Oral et al., found that additional elimination of fractionated potentials made AF non inducible and was predictive of a better long term result [42].

4. Follow up after Catheter Ablation for AF

The goal of treatment of AF is reduction of symptoms, improvement of the quality of life and the prevention of complications. A desirable result of catheter ablation for AF is an improvement in left ventricular function. An improved ejection fraction and decreases in left ventricular dimensions can be assessed with echocardiography [43]. For any electrophysiological ablation, absence of the arrhythmia treated, is the ultimate goal. The methods used for follow-up are extremely important in the assessment of the true incidence of arrhythmia recurrences because non symptomatic recurrences can be missed (table 2). Non symptomatic periods of AF can be demonstrated by using transtelephonic electrocardiographic monitoring [44]. Hindricks et al. [45], used continuous 7-day Holter to study the incidence of asymptomatic AF before and after PV isolation. They found that among the patients with AF after PV isolation the percentage patients with only asymptomatic periods was greater than among the patients with documented AF before ablation (37% versus 5% respectively). Using the Holter function of implanted pacemakers, Israel et al., found that in 38% of patients even long (more than 48 hours) periods of atrial tachycardia were asymptomatic [46]. These findings may have important consequences for example in the decision to continue or discontinue anticoagulation. Different techniques can be used to assess the impact on quality of life (QOL) after ablation. Arrhythmia specific questionnaires are advisable [47]. Significant improvement in the QOL after ablation was reported [48]. In some patients the implanted pacemaker offers an unique tool to assess the AF burden before and after ablation [49].

Differences in the definition of success, in the duration and intensity of the follow up, in the ablation techniques used and in the inclusion criteria for treatment, make comparison between studies difficult. Nevertheless the recently published international survey by Cappato et al. [50], provides important information in this and other aspects and deserves follow-up. Most groups, consider freedom of AF without anti-arrhythmic drugs as the definition of a successful treatment [51-53]. However, a significant reduction of symptoms with or without previously unsuccessful anti-arrhythmic drugs (AADs) can be a satisfactory endpoint for patients.

5. Conclusion:

It is almost certain that several mechanisms of AF exist [29]. Most authors now consider the initiation of AF to be the result of the interplay between triggers, such as PV foci, and a substrate such as areas of prolonged atrial refractoriness or delayed conduction [54]. The most common mechanism in patients is rapid firing from the pulmonary veins producing fibrillatory conduction. The persistence of AF results from different factors such as atrial dilatation and electrical and structural remodelling. Electrical and structural atrial remodelling plays an important role in the perpetuation of AF. Allessie demonstrated multiple wavelets in induced AF in goats [17] and it is therefore likely to be present in patients as well and responsible for the perpetuation of AF .

Based on these proposed mechanisms several non pharmacological interventions were developed. For the PV isolation developed by Haissaguere et al., the endpoint of the ablation is the electrical isolation of all 4 pulmonary veins. In the circumferential PV isolation developed by Pappone et al., the endpoint is a low peak-to-peak bipolar potential inside the lesion determined by local electrographic analysis and voltage maps. There are, however, strong arguments in favour of complete PV isolation in this approach as well. For the ablation proposed by Nademanee elimination of complex fractionated electrocardiograms is the goal. The influence of ablation on autonomic innervation is also assessable after different ablation techniques. Irrespectively of the technique used for AF ablation, the inability to induce AF after the procedure is a strong predictor for its long-term success [24,42,55,56]. Quality of life assessments, Holter ECG and event holter monitoring are of obvious importance in the follow-up. Incidental ECG's on an outpatient clinic or Holter-ECG's aren't enough to discover asymptomatic episodes of AF. However, for long term follow up assessment of stroke incidence and mortality are important. Mortality as an endpoint after PV isolation was only reported in a non randomised study [48]. Given the recent attention for lethal complications, randomised trials with conventional approaches, using appropriate endpoints are certainly needed.

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Table 1: Targets in catheter ablation for atrial fibrillation

Pathophysiologic target	Method	Goal
Trigger	Focal ablation	Electrical isolation of active PV's
Trigger and substrate	Intracardiac echo-guided ablation	Electrical isolation of antra with PV's
Substrate	Circumferential ablation	Voltage decrease within ablated area
Modulating Factors	Ablation vagal innervation	Elimination of the vagal response caused by rapid pacing
Substrate	Elimination of complex fractionated atrial electrocardiograms	Termination of atrial fibrillation

Table 2: Methods in the follow-up after ablation for AF

1. Electrocardiogram (ECG) based methods
-routine ECG on out-patient clinic
-Holter- ECG for 24 hours or even 7 days
-Event Holter-ECG on a daily basis or only in case of symptoms
-implantable recorders
-Holter function of pacemaker or ICD

2. Quality of Life assessments
-general questionnaires such as SF-36
-specific questionnaires

3. Functional assessments
-echocardiographic parameters of LV function
-neurohormones: plasma ANP and BNP levels

Legend: ICD: implantable cardioverter defibrillator, SF-36: short form 36 health survey, ANP/ BNP: atrial/ brain natriuretic peptide

Chapter 9

Right atrial linear ablation for paroxysmal AF guided by intracardiac echocardiography

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The Thoraxcentre Journal 2002;14:27-29

Right atrial linear ablation for paroxysmal AF guided by intracardiac echocardiography

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Introduction

Atrial fibrillation (AF) is an entity with a significant increase in mortality and morbidity including thrombo-embolic events, worsening of heart failure and is associated with a diminished quality of life. The main therapeutic options are maintenance of sinus rhythm (SR) or control of ventricular rate. Maintenance of SR with class Ia or class III anti-arrhythmic drugs (AADs) is a option, however the shortcoming of this approach is the potential pro-arrhythmic effect and the lack of efficacy. Rate control can be achieved either by drugs or by AV node ablation and permanent pacemaker implantation.

The aim of this case report is to demonstrate the possible role of a novel combined approach of ablation and drug therapy in maintaining sinus rhythm in a patient with highly symptomatic paroxysmal AF. The second aim is to show how intracardiac echocardiography can contribute to the efficacy of radio frequency (RF) catheter ablation.

Case presentation

A 58-year-old man presented with highly symptomatic paroxysmal AF (*Figure 1*) resistant to treatment with anti-arrhythmic drugs (AADs) including amiodarone. Despite treatment with varying AAD's during the past years he experienced long (several hours) attacks of palpitations every three days, accompanied by severe dyspnoea and occasionally angina. The patient had hypercholesterolaemia, hypertension and had coronary artery bypass operation five years earlier. He was referred for AV node ablation and permanent pacemaker implantation. On admission the patient was on amiodarone and metoprolol. Amiodarone was replaced by flecainide 100 mg BID, which didn't alter the frequency of tachycardia attacks.

On physical examination no coarse abnormalities, particularly any signs of heart failure, were found. His blood pressure was 180/80 mmHg. Echocardiography showed a slightly enlarged (50 mm) left atrium and a mildly depressed left ventricular function. Electrocardiography (ECG) showed sinus rhythm with a PR duration of 200 ms and a left bundle branch block (LBBB).

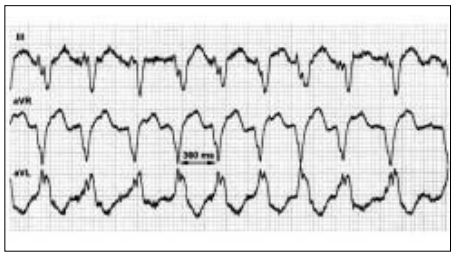

Figure 1. AF, rapid ventricular rate, LBBB

During palpitations, AF was recorded on a Holter-ECG with a high average ventricular rate (180 bpm) (*Figure 1*). A certain degree of "organisation" was detected (*Figure 2*). Because we wanted to avoid pacemaker implantation we proposed a modified radiofrequency catheter ablation (RF ablation) in two sessions.

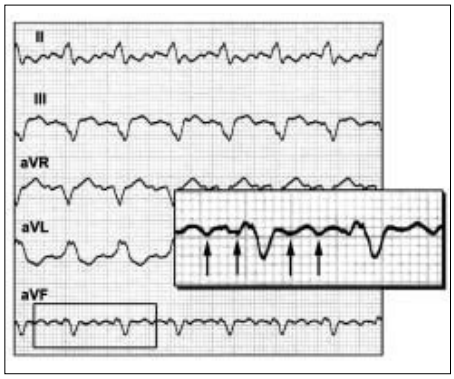

Figure 2. "Organisation" of the AF in to a flutter-like type arrhythmia

All surface ECG and intracardiac signals were recorded on a digital acquisition system (Cardiolab 4.0, Prucka Engineering, Inc., Houston, TX, USA). The RF current for focal and linear ablation was generated by a Stöckert generator (Cordis Webster, Baldwin Park, CA, USA) to achieve a tip-tissue interface temperature of 60 °C for up to 60 seconds.

RF ablation of the isthmus

In the first session, a 5 Fr decapolar electrode catheter (Supreme CS , Daig Corp, St Jude Medical Inc, Minnetonka, MN, USA) was advanced through the left subclavian vein and positioned in the coronary sinus (CS). Via the right femoral vein a 7 Fr steerable multipolar electrode catheter (Orbiter ST, Bard Electrophysiology, Billerica, MA, USA) was positioned in the right atrium along the anterolateral wall with the proximal electrodes at the level of the low atrial septum and the distal electrodes at the low right atrium close to the lateral edge of the cavo-tricuspid isthmus.

RF ablation of the inferior vena cava-tricuspid annulus isthmus was performed during sinus rhythm using an ablation catheter with a deflectable 8 mm tip (Conductor, Medtronic, Minneapolis, MN, USA). The target sites for RF ablation were selected using an anatomical approach. A line of overlapping lesions was created from the tricuspid valve towards the inferior caval vein. Success of ablation was assessed by demonstration of a bi-directional conduction block during pacing from the coronary sinus and low lateral right atrium after the isthmus ablation.

RF ablation of slow AV nodal pathway region

AV node modification was done using an ablation catheter with a 4 mm deflectable tip (Celsius D, Cordis Webster, Baldwin Park, CA, USA) introduced through the right femoral vein. The end point of AV node modification was set as appearance of a fast junctional rhythm during RF ablation.

Right atrial linear ablation

In the second session three multi-electrode catheters were inserted through a right femoral venous access. A quadripolar electrode catheter (Viking Cournand, Bard Electrophysiology, Billerica, MA, USA) catheter was introduced to record a stable His-potential. A bipolar pacing catheter (Bard Electrophysiology, Billerica, MA, USA) was positioned in the right ventricular apex. Three linear lesions in the right atrium were created using a novel RF ablation microcatheter system (3.7 Fr decapolar ablation catheter, Revelation T-x, Cardima Inc, Fremont, CA, USA) introduced through a long rigid vascular sheath (SR0, Daig Corp, Minnetonka, MN, USA). Lines between vena cava superior to vena cava inferior, vena cava superior to fossa ovalis and fossa ovalis to vena cava inferior were drawn. Successful ablation was defined as a clear reduction in the amplitude of the atrial signals.

Endocardial contact was secured continuously using intracardiac echocardiography (*Figure 3*) using an intracardiac echocatheter (ICE 9900, Boston Scientific Inc., San Jose, CA, USA) inserted through the left femoral vein and using a long sheath (Boston 5662, Boston Scientific Inc, San Jose, CA, USA). After RF ablation the patient continued his anti-arrhythmic medication. Four months after the treatment patient is without symptoms. A Holter-ECG showed continuous sinus rhythm with a occasional premature atrial contraction (PAC), but no AF or Afl. The PR time is 180 ms.

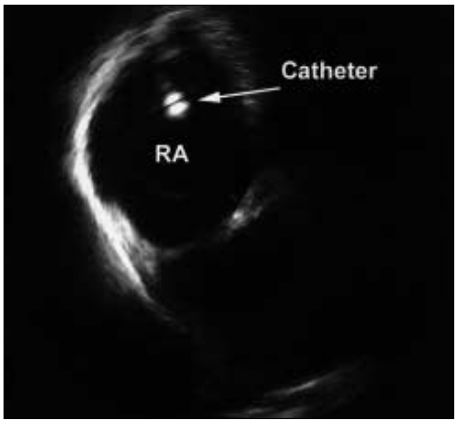

Figure 3a. Echocardiographic view showing the Revelation T-x ablation catheter without proper wall contact

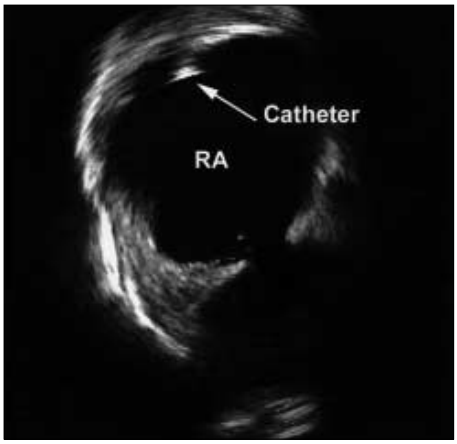

Figure 3b. Intracardiac echocardiographic view of the Revelation T-x ablation catheter in the right atrium showing good wall contact

Discussion

Atrial Fibrillation (AF) remains a challenge for every physician as it is an arrhythmia which affects a large proportion of the patients referred to the cardiologist.

Electrocardiographically AF is characterised by rapid, irregular, fibrillatory waves that vary in size and shape, mostly associated with an irregular ventricular response. The incidence of AF increases with age and is associated with a number of cardiac and non-cardiac

diseases. These diseases can result in an atrial abnormality, acting as a substrate necessary for the initiation of AF. Triggers include atrial premature beats, sympathetic and parasympathetic stimulation. For the persistence of AF perpetuating factors are required. Persistence may result from electrical and structural remodelling, characterised by atrial dilatation and shortening of the atrial ERP.[1] Atrial fibrillation and atrial flutter (AFl) are both intra-atrial reentrant tachycardias and frequently associated in an individual patiënt.[2,3] In AF multiple, small reentrant circuits (wavelets) are arising in the atria, colliding, being extinguished, and arising again.[4,5] A single macro re-entrant wave front exists in the case of AFl.

Spontaneous and pharmacological (class Ic and III anti-arrhythmic drugs) transformation of AF into AFl has been reported, suggesting a causative relation between the two in such cases. A certain amount wavelets and therefore a certain amount of contiguous myocardium is necessary to maintain AF. Catheter ablation for atrial fibrillation aims to compartmentalise the atria by the creation of linear lesions, thereby reducing the amount of contiguous myocardium necessary for the propagation of multiple activation wave fronts. This approach was supported by the success of the MAZE procedure.[6] Early attempts at creating right atrial linear lesions with conventional catheter tip technology provided limited success.[7] Although more efficacious, the creation of extensive left atrial lesions has been associated with a high rate of thromboembolic stroke.[8] The advantage of linear ablation as described above is that it is less time consuming then the standard techniques and it is likely that we can create more continuous linear transmural lesions by using such microcatheter system. As there is no direct evidence of successful ablation we used intra-cardiac echocardiography to ensure good wall-contact. Ablation of the inferior vena cava-tricuspid annulus isthmus reduces the frequency of recurrences in these patients.[9-11] Modulation of the AV node allows a long-term control of the ventricular rate and prevents the recurrence of severe clinical symptoms in more than 75% of patients with drug refractory AF.[12]

Other non-pharmacological therapies such as the MAZE procedure[6], catheter ablation of foci in the pulmonary veins[13] and the implantable atrioverter[14] can be considered. All these therapies are successful in specific patient groups but are too invasive (MAZE) or are still experimental with unknown long term (side) effects. Because our patient showed the combination of AF and pharmacological induced atrial flutter (AFl) it was decided to treat him with the above described combined ablation-pharmacological approach. Recent reports about right atrial linear ablation so far showed conflicting results, possibly due to inappropriate catheter design an/or insufficient wall contact of ablation catheters.[15-17] By using intracardiac echocardiography a better wall contact can be guarantied. This could explain the success of our approach. Further investigations are necessary to define the patient group in which this novel combined approach can be successful.

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Chapter 10

Electrical Isolation of pulmonary veins using cryothermal energy: study design and initial results

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Neth Heart J 2003;11:453-8

Electrical isolation of pulmonary veins using cryothermal energy: study design and initial results

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In the September 2003 issue of the Netherlands Heart Journal, the wrong figures where inserted in this article. The article is reprinted here with the correct figures.

Background. **Atrial fibrillation (AF) is the most frequently encountered arrhythmia. Radiofrequency pulmonary vein (PV) ablation is promising for symptomatic paroxysmal AF, but is associated with a significant risk of PV stenosis.**
Objectives. **To assess the efficacy of cryothermal PV ablation and the incidence of PV stenosis.**
Methods. **Highly symptomatic patients with paroxysmal or persistent AF were eligible for cryothermal ablation. Multislice spiral CT scans were performed before, and three months after ablation. AF burden was assessed using transtelephonic ECG recording and by telephone enquiry.**
Results. **An attempt was made to isolate 27 PVs in 15 patients. In total, 20 PVs could be isolated (74% acute success). No significant difference in PV diameter was seen before and after ablation. Five out of 12 patients with paroxysmal AF were completely without AF after one ablation procedure. An additional two patients reported a significant reduction in symptoms. In the three patients with persistent AF no improvement was reported.**
Conclusion. **Cryothermal PV ablation was effective in isolation of the targeted PVs. It appears to be safe, as no PV stenosis was seen in this study three months after the ablation. Taking into account a learning curve, we consider the clinical results to be very promising. (*Neth Heart J* 2003;11:453-8.)**

Key words: atrial fibrillation, cryo-thermal ablation, pulmonary veins, stenosis

Atrial fibrillation (AF) is the most frequently encountered sustained arrhythmia in clinical practice. The pulmonary veins are an important source of ectopic beats, which appear to be the main initiator of paroxysms of atrial fibrillation.[1] The myocardial architecture (arrangement of myocardial cells, fibrosis) in normal pulmonary veins is highly variable and responsible for non-uniform anisotropic properties.[2] Successful surgical treatment of AF always includes isolation of the pulmonary veins.[3,4] Empiric catheter-based pulmonary vein (PV) isolation appears to be a promising approach for maintaining sinus rhythm in patients with paroxysmal AF.[5,6] However, the procedure is associated with a significant risk (4 to 8.9% of treated patients) of pulmonary vein stenosis, defined as a luminal diameter reduction of 50% or more.[7-11] Luminal diameter reduction between 25 and 50% was found in 16% of treated patients.[7] PV stenosis can be life-threatening.[12] The aims of our study were twofold. Firstly we wanted to assess the efficacy of cryothermal PV ablation. A further objective was to measure the incidence of PV stenosis using cryothermal energy.

Methods

Patients with a history of problematic AF referred to the department of clinical electrophysiology were considered candidates for this single-centre prospective study. Initially, patients with persistent AF were also included. Entry criteria for paroxysmal AF included symptomatic episodes, occurring at least monthly, despite the use of more than two antiarrhythmic drugs. Exclusion criteria included severe valvular disease, marked left atrial enlargement (>50 mm, measured on M-mode echocardiography) and contraindications for oral anticoagulation. The day before the procedure a transoesophageal echocardiogram was performed to

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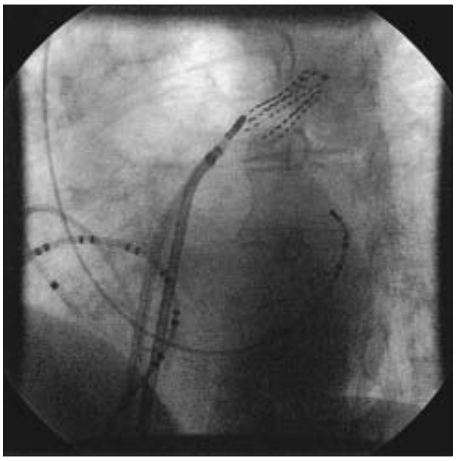

Figure 1. Basket catheter positioned together with the ablation catheter in the left upper pulmonary vein.

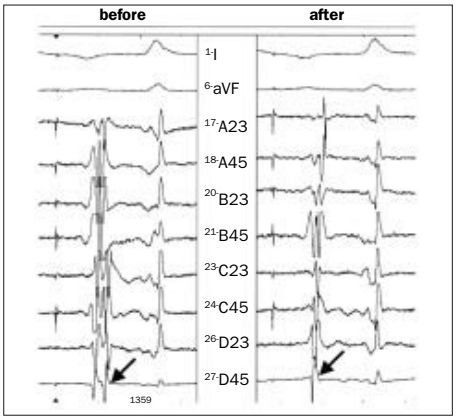

Figure 2. Pacing in the coronary sinus before and after successful ablation. In the left panel an atrial signal followed by a pulmonary vein potential is seen. In the right panel the pacing signal is only followed by an atrial signal.

exclude left atrial thrombi. Antiarrhythmic drugs were continued.

Ablation

During the first ablation procedures an attempt was made to isolate the left upper PV (LUPV) and right upper PV (RUPV). A decapolar catheter was inserted in the coronary sinus (CS) via the left subclavian vein. A bipolar catheter was advanced in the right ventricular apex and was used as the reference catheter for a 3D positioning system (Localisa).[13] Double transseptal puncture was performed guided by intracardiac echocardiography.[14] After transseptal puncture the patients were heparinised, guided by the activated clotting time (ACT). After making a selective venogram a multipolar basket catheter (Constellation,

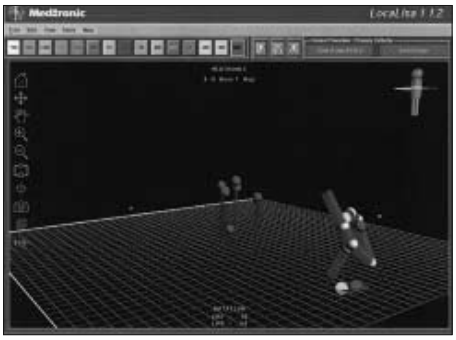

Figure 3. Use of the Localisa 3D positioning system. On the left side of the image the positions of ablation applications in the right upper pulmonary vein are saved. On the right side of the image a ring of electrodes from the Basket catheter in the left upper pulmonary vein (LUPV) is made visible. The ablation catheter is seen within this ring at the position of the first cryothermal application in the LUPV.

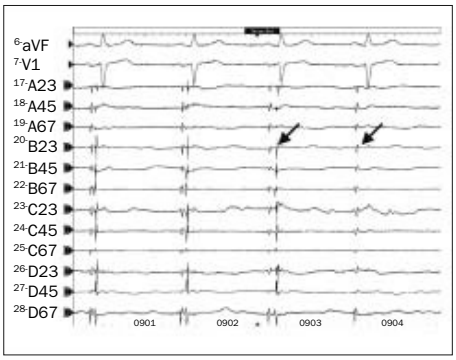

Figure 4. Disappearance of pulmonary vein potentials (PVP) during ablation. The first three atrial potentials during sinus rhythm are followed by a PVP. The last atrial potential is no longer followed by a PVP. This PVP did not return and this pulmonary vein was therefore successfully electrically isolated.

Table 1. Patient characteristics before catheter ablation.

No.	Gender	Age (years)	Paroxysmal/ persistent	Cardiac disease	Attack pattern	Cardioversions before	Cardioversions after
1	Male	63	1	-	M	15	1
2	Male	57	1	DCM	D	1	0
3	Male	56	1	-	D	0	0
4	Female	68	1	Thyroid	W	0	1
5	Male	51	2	-	P	3	0
6	Male	59	1	-	W	8	0
7	Female	62	1	Thyroid	D	0	0
8	Male	52	1	-	D	1	0
9	Female	40	1	Valv.	W	0	0
10	Male	56	1	H/DM	M	7	0
11	Male	50	2	H	P	1	0
12	Male	40	1	Thyroid	P	15	1
13	Male	53	1	Valv.	D	2	0
14	Male	45	1	-	D	1	1
15	Female	40	1	-	W	0	2

1=paroxysmal, 2=persistent, D=Daily, DCM=dilated cardiomyopathy, DM=diabetes mellitus, H=hypertension, M=monthly, Valv=valvular disease, W=weekly.

Boston Scientific, Natick, MA, US) was advanced into the pulmonary vein (figure 1). The electrical connection between left atrium (LA) and PVs before and after ablation was studied while pacing from the CS (figure 2). Positioning of the ablation catheter within the PV was guided by fluoroscopy, electrograms and the Localisa system (figure 3).The pulmonary veins were ablated at the venoatrial junction, aiming at electrical isolation of the veins (figure 4). Ablation was performed with a 7-French 6 mm tip Freezor-Xtra cryocatheter (Cryocath Technologies Inc., Kirkland, Quebec, Canada). Applications lasted four minutes each. After the ablation, patients were hospitalised for at least two days and followed for

Table 2. Ablation data.

No.	LUPV	Diam. (mm)	Appl. (no.)	Isolated	RUPV	Diam. (mm)	Appl. (no.)	Isolated	LIPV	Diam. (mm)	Appl. (no.)	Isolated
1	+	18	2	+	-	17			+	17	3	+
2	+	15	13	-	+	15	NA	-	-	21		
3	+	19	16	+	-	19			-	19		
4	+	21	17	+	-	18			+	19	2	+
5	+	18	3	+	+	NA	8	-	-	17		
6	+	15	NA	+	+	19	10	+	-	15		
7	+	NA	6	+	+	NA	5	+	-	NA		
8	+	18	8	+	-	18			-	18		
9	+	NA	6	+	+	NA	5	+	-	NA		
10	+	NA	3	+	-	NA			+	NA	8	+
11	+	22	7	+	+	18	5	-	-	18		
12	+	22	NA	-	+	18	NA	+	-	17		
13	+	19	0		+	18	13	-	-	17		
14	+	21	11	+	+	19	8	+	-	13		
15	+	15	9	+	+	17	15	+	-	15		

Appl.=application, diam=diameter, LIPV=left inferior pulmonary vein, LUPV=left upper pulmonary vein, NA=not available, RUPV=right upper pulmonary vein.

Table 3. Additional procedure data and follow-up.

No.	Isthmus	Remarks	Proc. time (minutes)	Fluroscopy (minutes)	Complications	Type	Attack pattern
1			249	72.8	yes	PE, no puncture	–
2			322	68.8			D
3			364	80.3			W
4			212	56.3			W
5			281	58.9			D
6			396	110	yes	hypotension	–
7			194	45.3			D
8			335	69.1			D
9			254	49.5			–
10	+		255	64.3			–
11	+		227	45	yes	ST elevation inferior	
12			297	59.4			D
13			297	55.1	yes	ST elevation inferior Amaurosis fugax	D
14	+	one left vein	299	53.6	yes	ST elevation inferior	–
15			272	50.2			M

D=daily, M=monthly, PE=pericardial effusion, Proc.=procedure, W=weekly, +=associated flutter ablation and cavo-tricuspid isthmus block achieved, – =no AF attacks after PV ablation.

early recurrences. Heparin was continued and anticoagulation treatment (acenocoumarol) started. If the patients remained symptomatic after three months the persistence of electrical isolation of the successfully treated PVs was to be confirmed, and the other PVs ablated.

Follow-up
In-hospital recurrences of AF were documented. After discharge the patients were followed in the outpatient clinic on a regular basis. Transtelephonic ECG recordings were made weekly and in case of symptomatic arrhythmias. Furthermore at three months, the patients were interviewed by telephone by a research nurse about their subjective wellbeing. Before, and three months after the ablation, the diameter of all pulmonary veins was measured using multislice spiral CT scans. A one-year CT scan is scheduled in all patients.

Results

Patients
Results from the first ablation of the initial 15 patients included in this study are reported. Their demographic and clinical data are summarised in table 1. The mean age was 52.8 years (40 to 68 years), and four were female. Their mean LA size measured with M-mode echocardiography was 40.9 mm (30 to 48 mm). Ten patients had been cardioverted once or more in the past and six of them had daily attacks of AF.

Ablation
Acute results of the ablation are shown in table 2. An attempt was made to isolate 27 PVs, of which 20 veins could be isolated (74% acute success). The mean fluoroscopy time was 62.6 minutes and the mean procedural time 285 minutes (table 3). An average number of 7.71 (1 to 17) applications per vein was necessary.

Although it was the intention to treat only the LUPV and RUPV, because of procedural reasons the left inferior PV (LIPV) was occasionally targeted instead of the RUPV (n=2) or as a third PV (n=1).

Multislice spiral CT scan
Using multislice CT angiography (MSCT) of the treated vessels no significant difference in PV diameter before and three months after PV ablation was seen: LUPV 18.58x2.61 mm versus 18.13x2.10 mm; LIPV 17.17x2.12 mm versus 17.00x3.59 mm; RUPV 17.55x1.44 mm versus 18.19x0.95 mm.

Complications
Complications are shown in table 3. One patient had a pericardial effusion, not requiring puncture. Temporary ST-segment elevation in the inferior leads after selective angiography of the PV (LUPV and RUPV) was seen in three patients. In one patient a very short episode of blurred vision occurred on the second day after the procedure. No other complications occurred.

Follow-up

Mean follow-up was 276 days (104 to 426 days). Five of 12 patients (42%) with paroxysmal AF were completely without AF after one ablation procedure. An additional two patients (17%) reported a 50% reduction in symptoms. In the three patients with persistent AF no improvement was reported. The evolution in the AF burden is shown in table 3.

Discussion

It has been shown that extensions of atrial muscle surrounding the pulmonary veins (PVs) can have ectopic electrical activity able to trigger AF.[1,2,15-17] The long-term success rate of RF ablation (RFA) to cure AF by targeting these initiators using a focal approach is low (29%).[18] Empiric PV isolation appears to be a more effective approach to the maintenance of sinus rhythm.[5,6] Although distal isolation can be achieved with fewer lesions, ostial isolation is required in the majority of patients to eliminate arrhythmogenic activity and AF.[18] It has become clear that electrical isolation of all four pulmonary veins from the left atrium provides the best cure rate. However, this is associated with a significant risk of pulmonary vein stenosis,[9-11] which has serious consequences, and can occur very late after the procedure (1 to 2 years).[8]

Cryothermal ablation

Cryothermal tissue injury is distinguished from hyperthermic injury, such as caused by RF energy, by the preservation of basic underlying tissue architecture and minimal thrombus formation. We hypothesised that using cryothermal energy would prevent the occurrence of PV stenosis. Cryothermal ablation, with a different set-up, was formerly used for this indication and seems to be safe.[19]

Results of PV ablation

Reported results of PV ablation show a large variability and are also dependent on the definitions used for the endpoints. Recently Oral et al.[20] reported results of PV ablation (with at least three PVs ablated) in 70 patients. After a mean follow-up of five months 70% of the patients with paroxysmal AF were in sinus rhythm (SR), compared with only 22% with persistent AF. A lower success rate of 51% after a mean follow-up of nine months was reported by Deisenhofer.[11] Gerstenfeld et al.[10] reported a very high recurrence rate of 68%. After 10.4±4.5 months, 85% of patients with paroxysmal AF and 68% of patients with permanent AF were in SR in a report by Pappone[21] using circumferential RF ablation.

Complications of PV ablation/PV stenosis

The risk of pulmonary vein (PV) stenosis after PV ablation is significant.[22,23] Metaplasia, proliferation, thrombosis and neovascularisation may lead to PV stenosis after RF energy application around or inside the PV ostia.[9] Pulmonary vein stenosis is potentially life-threatening.[24] The clinical manifestations of PV stenosis consist of chest pain, dyspnoea, cough, haemoptysis, recurrent lung infection and pulmonary hypertension. PV stenosis can be asymptomatic. Some patients may show late progression of PV stenosis during follow-up.[8,9] In a recent series of 380 ablated veins, the CT scans revealed 2 PVs (1%) with severe (>70%) stenosis, 13 (3%) with moderate (51 to 70%) stenosis, and 62 (16%) with mild (≤50%) stenosis.[7] In a recent report on 75 patients, Deisenhofer found stenosis of 25 to 50% in 9.3% patients and of >50% in 8.9% patients.[11] Others estimate the incidence of PV stenosis (defined as luminal diameter reduction >50%) detected by spiral computer tomography scan or three dimensional magnetic resonance angiography) at 0 to 7% per PV ablated.[9]

Moderate PV stenosis (50% narrowing) was observed in one of 136 consecutive patients (0.7%) after RF ablation of PV using an irrigated-tip catheter.[25] Using cryothermal ablation Rodriguez[19] found no stenosis after PV ablation in 53 veins. PV stenosis can be treated with balloon dilation, although the long-term course is unknown.[26]

Pericardial effusion

Pericardial effusion is reported in almost all reports about PV ablation.[27] Deisenhofer reported pericardial effusion in 4 of 75 patients (5.3%).[11] We suspect that catheter manipulation within the left or right atrium or damage to the thin-walled left atrial appendage is responsible.

Other complications of PV ablation

Other less frequently described complications such as phrenic nerve paralysis and reflex bradycardia were not observed in our series.[28]

Future perspectives

Several authors have explained the modest effect of PV ablation by the existence of non-PV foci.[29,30] Repeat ablation procedures are necessary in almost 50% of patients.[25] The role of concomitant cavotricuspid isthmus ablation and creation of a linear lesion (referred to as the 'lateral mitral isthmus line') between the ostium of the left inferior PV and lateral mitral annulus[25] needs to be defined. These lesions may reduce the amount of atrium available to support multiple wavelet reentry, changing the substrate for AF.

Conclusion

This report shows the initial results of the first patients in our department ever treated with PV ablation for paroxysmal AF. In 5 of 12 (42%) patients with paroxysmal AF no recurrences of AF occurred. An additional 2 of these 12 (17%) reported a 50% reduction in symptoms. Taking into account a learning curve, we consider these results promising. Cryothermal PV ablation appears to be a safe method. No PV stenosis was seen in this study three months after the ablation.

Numbers are, of course, still too low to make firm conclusions. However the absence of pulmonary vein stenosis three months after ablation of 27 veins is encouraging. Furthermore this report is about the initial procedure in every patient. Of interest is that it appears there is a subset of patients who report a significant improvement in AF burden after PV ablation although AF did return. All patients with recurrence of AF were offered a second procedure to evaluate invasively the results of their first treatment and to extend the ablation to the two inferior PVs. ■

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Chapter 11

Sixteen-row multislice computed tomography in the assessment of pulmonary veins prior to ablative treatment: validation vs conventional Pulmonary venography and study of reproducibility

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Eur Radiol 2004;14:369-374

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Sixteen-row multislice computed tomography in the assessment of pulmonary veins prior to ablative treatment: validation vs conventional pulmonary venography and study of reproducibility

Received: 7 July 2003
Revised: 3 October 2003
Accepted: 8 October 2003
Published online: 14 November 2003

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Abstract The aim of this study was to validate multislice computed tomography (MSCT) venography measurements of pulmonary vein (PV) diameters vs conventional pulmonary venography (CPV), and to assess the reproducibility of MSCT data. The study included 21 consecutive patients with atrial fibrillation who were planned for cryothermal ablation of PVs. One day before ablation, all patients underwent CPV and contrast-enhanced non-gated MSCT venography. The MSCT was repeated 3 months after ablation. The CPV images of the treated PVs (n=40) were analyzed and compared with the results of MSCT measurements. Reproducibility of MSCT venography-based data was assessed by interobserver (n=84 PVs) and interexamination (n=44 PVs) variability. Pre-treatment PV diameters on MSCT and CPV showed good correlation (r=0.87, p<0.01; 18.9±.2.3 mm, 188.5±.2.4 mm, respectively). Interobserver agreement and interexamination reproducibility were good (r=0.91, r=0.82, respectively, p<0.01), with narrow limits of agreement (Bland and Altman method). The MSCT venography allows accurate and reproducible assessment of PVs. It can be used both in non-invasive planning of treatment for ablative therapy and in the follow-up of patients.

Keywords Computed tomography · Venography · Pulmonary veins

Introduction

Measurement of pulmonary vein (PV) diameters is important in patients treated for atrial fibrillation. Transcatheter radio-frequency ablation is increasingly being used for treatment of lone atrial fibrillation [1]; however, the incidence of significant PV diameter reduction after the treatment is relatively high, up to 18.1% per treated vein, and this is a major concern [2]. Accurate measurement of PV diameter is therefore important in the follow-up of these patients.

The latest generation of 16-row multislice computed tomography (MSCT) scanners has improved non-invasive diagnostic imaging especially for various angiographic applications [3]. Due to the improved volume coverage speed, and sub-millimetre spatial resolution with isotropic voxels that allow 3D reconstructions in any plane without loss of spatial resolution, 16-row MSCT angiography might be also useful for the routine evaluation of PV diameters before transcatheter ablative treatment; however, there has been no published evidence on validation of MSCT venography for this purpose, nor on the reproducibility of the method; therefore, the aims of this study were to: (a) validate 16-row MSCT venography in the assessment of PVs diameter prior to PVs ablation treatment in comparison with conventional pulmonary angiography; and (b) evaluate MSCT reproducibility.

Materials and methods

Study population

We prospectively enrolled 21 consecutive patients (14 men and 7 women; mean age 53.2±7.6 years) who were referred for cryother-

mal energy ablation of PVs, to treat paroxysmal atrial fibrillation occurring at least monthly and refractory to more than two antiarrhythmic drugs. Patients with severe valve disease, marked left atrial enlargement (>50 mm, measured on M-mode echocardiography) and contra-indications for oral anticoagulation were excluded. As a routine work-up, all patients underwent clinical examination, transesophageal echocardiography and electrophysiological studies before ablation. For the purpose of this study, MSCT pulmonary venography was performed 1 day before and 3 months after ablative treatment. The study was approved by the Institutional Review Board and all patients gave written informed consent for the procedures.

Conventional radiographic PV angiography and quantitative vessel analysis

In all patients selective conventional pulmonary venography of PVs planned for cryothermal ablation was performed by injection of 5–10 ml of contrast material prior to the treatment. Digitized angiographic images of PVs were used for visualization and diameter measurements with quantitative coronary analysis software (Fig. 1; CAAS II, Pie Medical Equipment B.V. Maastricht, The Netherlands). The PVs were measured from anteroposterior images at the projected ostium by two experienced investigators. Measurements were made in the still frame that best showed the PV ostium. The diameter of PV ostium was the distance between junction of the upper wall of the PV and the wall of the left atrium, and junction of the lower wall of the PV and the wall of the left atrium. The mean value of these two measurements were used in the statistical analysis.

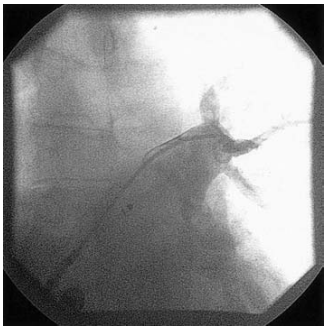


Fig. 1 Selective pulmonary venography of the left superior pulmonary vein in anteroposterior projection

MSCT pulmonary venography

Multislice CT pulmonary venography was performed using 16-slice MSCT scanner (Sensation 16, Siemens, Erlangen, Germany), 1 day before the PV ablation and at 3 months follow-up. The scan range was from the aortic arch to the lower margin of the heart (range 140–180 mm), imaged during a single 3- to 5-s breath hold. We did not use ECG gating for image acquisition. A bolus of 60 ml nonionic contrast material (Iodixanol 320 mgI/ml; Visipaque, Amersham Health, UK) was injected into the cubital vein using a power injector set at 3 ml/s. Whenever the signal density level in the ascending aorta, which was monitored every 1.25 s, reached a predefined threshold of +100 HU above baseline, the patient was automatically instructed to maintain an inspiratory breath hold during which the MSCT data were acquired. Scan parameters were: detector collimation 16×1.5 mm; table feed 48 mm s^{-1}, 120 kV, 120–140 mAs (depending on the patient size), rotation time 500 ms, and estimated radiation exposure between 3.1 and 4.1 mSv [4]. Axial images were reconstructed with the following parameters: effective slice width 1 mm; increment of reconstruction 0.6 mm; field of view 250 mm; and de-convolution algorithm medium.

Image analysis

Multislice CT and conventional pulmonary venography images were reviewed in random order by two experienced independent investigators who were blinded to the patient's identity and site of performed ablation. Each of the investigators reconstructed an image dataset for multiplanar reconstructions with maximum intensity projection (MIP) algorithm to create the best orientation along the axis of the PVs for orthogonal measurements. The best view to demonstrate PVs was the oblique coronal projection with cranial and caudal rotation (Fig. 2). The MIP algorithm with curved con-

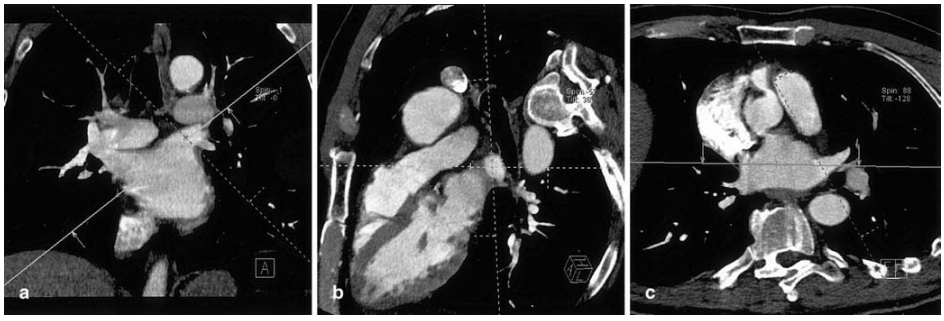


Fig. 2a–c In the same patient, multislice computed tomography (MSCT) pulmonary venography. **a** Coronal projection of the left superior pulmonary vein planned for ablation. **b** Sagittal and **c** axial projection of the same vein

figuration was used to trace a drainage pattern of PVs into the left atrium. The exact PV diameter at the ostium may at times be difficult to assess by imaging techniques because there is no exact and clearly visible transition from PV to the left atrium [5]. In this study, the PV ostium was defined by the intersection of tangents of the PV in oblique coronal projection with cranial and caudal rotation and the adjacent wall of the left atrium.

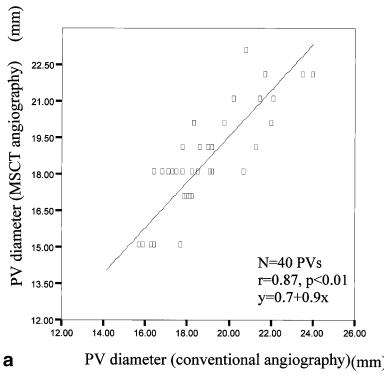
Statistical analysis

Continuous variables (PV diameters) were described by mean± SD. Categorical variables (number of treated and non-treated PVs) were presented as frequencies. The MSCT and conventional pulmonary venography measurements were compared by linear regression. Using Bland-Altman plots, agreement between two methods was assessed [6]. To evaluate the interobserver reproducibility of MSCT venography-based data, diameters of all PVs on the pre-procedural MSCT scans were measured by two independent observers in a blinded fashion. For interexamination variability, diameters of non-treated PVs were measured on the pre-procedural and the follow-up MSCT examination. The interobserver and interexamination variability was analyzed by correlation and Bland-Altman method. Differences in PV diameters between MSCT and conventional venography, measurements between the two observers and between preprocedural and follow-up MSCT examinations were tested for statistical significance by paired Student's *t* test. A statistics software package (SPSS release 11.0, Chicago, Ill.) was used for the analysis.

Results

Using 16-row MSCT pulmonary venography, images of excellent quality for quantitative assessment were obtained in all 21 patients, with scanning time of 3–5 s and average in-room time of 5–6 min. No adverse reactions to intravenous contrast material were encountered. A total of 84 PVs were studied on MSCT. Using conventional pulmonary venography, 40 of 84 (47.6%) PVs were visualized for cryothermal ablation and these data were used for validating the corresponding MSCT data.

Average diameter of the isolated PVs on MSCT angiography and conventional pulmonary venography are presented in Table 1. There were no significantly different measurements between MSCT angiography and conventional venography, the average diameter of the targeted PVs being 18.9±2.3 vs 18.5±2.4 mm, respectively, with high correlation r=0.87, p<0.01; y=0.7+0.9x (Fig. 3a); however, since high correlation does not assure that the two methods agree perfectly, Bland-Altman analysis was performed. This analysis is based on a plot of difference against means which allows one to investigate any possible relationship between the measurement error and the true value. The Bland-Altman plot (Fig. 3b) revealed good agreement between MSCT pulmonary venography and conventional venography. All data were covered by limits of agreement 2 SD wide, indicating that MSCT venography can be used in place of conventional venography.



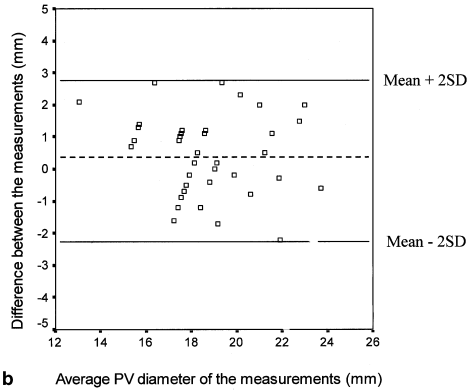
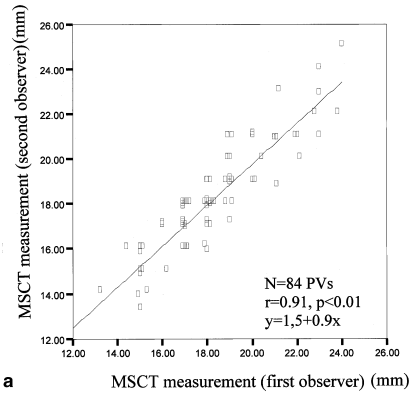


Fig. 3 **a** Correlation between MSCT and conventional radiographic pulmonary venography. **b** Bland-Altman plot. Difference between pulmonary vein diameter measured by conventional radiographic pulmonary venography and MSCT venography is plotted against the mean of individual diameters

Table 1 Pre-procedural diameters of the target pulmonary veins. *MSCT* multi-slice computed tomography, *CPV* conventional pulmonary venography

Pulmonary vein (*n*)	MSCT (mm)	CPV (mm)	*p*
Left superior (21)	18.6±2.9	19.1±2.4	n.s.
Left inferior (4)	18.7±1.7	18.6±2.1	n.s.
Right superior (15)	18.5±1.9	18.7±2.4	n.s.
Right inferior (0)	–	–	–

To quantify interobserver agreement of MSCT venography, diameters of all PVs (n=84) were measured by two observers on the pre-procedural MSCT examination. The data showed high correlation (r=0.91, p<0.01;



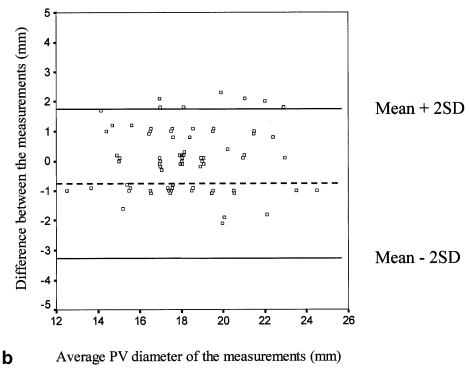
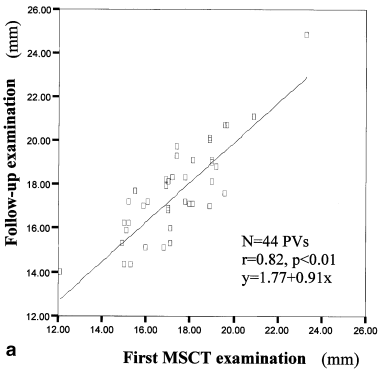


Fig. 4 **a** Correlation between MSCT measurements by the two independent observers. **b** Bland-Altman plot for interobserver variability. Comparison of pulmonary vein diameters between the two observers. *Dashed line* indicates the mean differences between the investigators



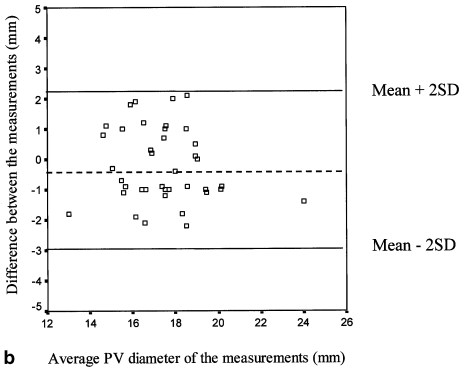


Fig. 5 **a** Correlation between MSCT measurements of the non-treated pulmonary veins on the first and the follow-up examinations after 3 months. **b** Bland-Altman plot for interexamination variability. Comparison of pulmonary veins dimensions between the two examinations. *Dashed line* indicates the mean of differences between the investigators

y=1.5+0.9x) and there was no significant difference in PV diameter among the two measurements (paired Student's t test, p>0.05), with average PV diameter of 18.2±2.4 mm (first observer) and 18.1±2.3 mm (second observer; Fig. 4a). Bland-Altman plot (Fig. 4b) indicated good agreement between the observers. The difference between the two measurements (dashed line in Fig. 4b) is close to zero, and the limits of agreement are narrow.

To study interexamination variability of MSCT venography measurements, we compared the non-treated PVs (n=44) based on the preprocedural MSCT and the follow-up examination at 3 months follow-up. The paired measurements based on the two sequential MSCT examinations showed high correlation (r=0.82, p<0.01; y=1.8+0.9x) and there was no significant difference in PV diameter (paired Student's t test, p>0.05), with average PV diameter of 17.3±1.9 mm in the first examination and 17.5±2.1 mm in the second examination (Fig. 5).

Discussion

The current study indicates that non-cardiac-gated 16-row MSCT venography is a robust, reliable, and repro-

ducible imaging modality for non-invasive evaluation of PV anatomy and diameters. The MSCT-based PV diameter measurements were similar to those obtained with the standard of reference, conventional pulmonary venography using quantitative vessel analysis, and MSCT yielded comparable measurements during repeated examinations.

Presence of diameter reduction of PVs has been measured using different noninvasive and invasive methods, including intracardiac ultrasound [7], conventional pulmonary venography [8], transoesophageal echocardiography [9], MR imaging [10], as well as spiral and multislice CT [11, 12, 13, 14]. To the best our knowledge, there are no previous reports establishing the validity and/or reproducibility of PV-diameter measurements based on MSCT pulmonary venography; however, the use of MSCT venography has been mentioned/proposed in three recent studies for follow-up of patients after the treatment of PVs with radio-frequency ablation, suggesting good correlation with conventional venography data [7, 8, 11].

This study demonstrated good reproducibility of multislice acquisition with 16-row detectors as verified by limits of agreement and good correlation between two investigators. The 16-row MSCT allowed fast coverage (3–4 s) of the entire anatomic territory of the PVs free of respiratory motion. Moreover, the increased scanning speed allowed the use of thin slices (1 mm) with good in-plane (axial) and through-plane (longitudinal) resolution of the examined section and good visualization of PVs. Unlike in the study of Trabold et al. [12], we did not perform MSCT examination with ECG retrospective gating to exclude cardiac motion artifacts. Refraining from ECG gating did not interfere with the image quality of PVs, probably because the atria and pulmonary veins do not show as marked cardiac motion as the ventricles. Our rationale for not using ECG gating is that this adds to the ease and simplicity of the examination and markedly reduces radiation exposure [15].

Morphology and diameter of the proximal 20 mm distal to the ostium were evaluated by MIP algorithm which was demonstrated to be reliable in evaluation of anatomic characteristics and diameter of blood vessels. This technique enables examination of the PVs morphology and visualization in coronal, axial, and sagittal planes. An advantage of MIP over multiplanar reformation is in the possibility to visualize the entire structure even if it is not in a single plane. Ablative treatment of PVs was applied in all segments of the circumference of imaged PV if needed; therefore, visualization in three projections is important for monitoring possible diameter reduction during the follow-up period. Conventional venography of PVs may be limited in this respect since only the anteroposterior projection view is shown [16]. This especially refers to the left PVs, which tend to be oval in shape, with their short axis oriented approximately in the anteroposterior direction so that anterior or posterior sections of the ostia remains undetectable on conventional venography. Also, PVs are not accurately delineated and inferior PVs are often overlapped by other structures resulting in inadequate visualization [17, 18].

Conclusion

We conclude that non ECG-gated MSCT pulmonary venography with a 16-row MSCT scanner provides reliable visualization of PVs during a single 3- to 5-s breath hold with possibility for quantitative assessment. The MSCT is non-invasive, easily reproducible, and suitable for visualization of PVs during the long-term follow up of the patients who have undergone ablative treatment.

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Chapter 12

Sixteen-row multislice computed tomography of pulmonary veins: 3-months follow-up after treatment of paroxysmal atrial fibrillation with cryothermal energy

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Eur Radiol 2005;15:1122-1127

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Sixteen multidetector row computed tomography of pulmonary veins: 3-months' follow-up after treatment of paroxysmal atrial fibrillation with cryothermal ablation

Received: 13 August 2004
Revised: 12 January 2005
Accepted: 18 January 2005
Published online: 19 February 2005

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Abstract The aim of the study was to assess pulmonary veins (PVs) for the presence of stenosis 3 months after cryothermal ablation (CA) with a new method of electrical isolation of PVs using contrast-enhanced 16 multidetector row computed tomography (MDCT). Twenty four patients with symptomatic atrial fibrillation underwent CA in 46 PVs. MDCT of PVs was performed before the treatment and after 3-months' follow-up. Following cryoablation, 13/24 (54%) patients showed clinical improvement and had reduced attacks of atrial fibrillation. The dimensions of the treated PVs remained unchanged: the coronal ostial diameter was 19.1±2.4 preprocedural versus 18.6±2.4 mm at follow-up, $p>0.05$; the ratio of the coronal and axial diameters at the ostium was 1.2±0.2 versus 1.2±0.1, $p>0.05$, respectively, and the coronal diameter of the proximal 10 mm was 17.1±2.5 mm versus 16.5±2.2 mm, $p>0.05$, respectively. CA is a promising technique for electrical isolation of PVs that has not been associated with stenosis at the orifice and the proximal 10 mm of the PVs after 3-months' follow-up. MDCT is a noninvasive, fast and comfortable method for assessment of PVs in a three-dimensional manner prior to ablative treatment and during the follow-up.

Keywords Computed tomography · Pulmonary veins · Arrhythmia

Introduction

Most arrythmogenic foci in patients with paroxysmal atrial fibrillation refractory to medical therapy are located within pulmonary veins (PVs). Electrical disconnection of the veins from the left atrium using radiofrequency ablation is considered to be a major breakthrough in treatment of these patients [1]. However, radiofrequency ablation in the vicinity of the ostia is associated with a risk of PV stenosis after the procedure and during the follow-up period (up to 42.0% depending on the technique and method of assessment) [2]. Although usually asymptomatic, PV stenosis could progress to complete occlusion with severe and potentially life threatening symptoms of segmental pulmonary hypertension or venous infarction of the corresponding lobe [2, 3].

Cryothermal ablation (CA) is a promising new method in the treatment of paroxysmal atrial fibrillation [4], and has been successfully used in patients with atrioventricular nodal reentrant tachycardia and ablation of the atrial and ventricular myocardium [5, 6]. However, the possibility of PV stenosis after the treatment remains a major concern, and assessment of PV dimensions before and after CA is necessary to evaluate this technique. Two studies have been published on the long-term outcome in these patients with different clinical success [7, 8].

The aim of the study was to evaluate the treated PVs for any potential diameter reduction by comparing the three-dimensional imaging data sets from contrast-enhanced 16 multidetector row computed tomography (MDCT) of PVs, before CA and after 3-months' follow-up.

Materials of methods

Study population

The prospective study included 24 patients (mean age 52.4± 8.1 years, 19 males) with paroxysmal atrial fibrillation occurring at least monthly and refractory to more than two antiarrhythmic drugs, with 46 treated vessels. The study was designed with 90% power to detect minimal reduction of the diameter of PVs. Patients with severe valvular disease, marked left atrial enlargement (larger than 50 mm, measured by M-mode echocardiography) and contraindications for oral anticoagulation were excluded from the study. All patients underwent clinical examination, transesophageal echocardiography, electrophysiology study, transcatheter pulmonary angiography and MDCT of PVs before CA. The study was approved by the institutional ethical committee and the patients signed a written informed consent for the procedures.

Guiding studies to target ablative treatment

A decapolar catheter was inserted into the coronary sinus, while a bipolar catheter was placed in the right ventricular apex as the reference catheter for the three-dimensional positioning system Localisa (Medtronic, Minneapolis, MN, USA) [9]. Double transseptal puncture was guided by intracardiac echocardiography [10] with administration of heparin to maintain an activated clotting time of more than 250 s. A multipolar basket catheter (Constellation, Boston Scientific, Natick, MA, USA) was positioned into the target PV. The selection of the PV for CA was based on clinical and/or electrophysiologic assessment. The electrical connection was studied between the left atrium and the target PV before and after CA during pacing from the coronary sinus.

CA procedure

Ablation was done with a 7-French Freezor-Xtra cryocatheter (Cryocath Technologies, Kirkland, Quebec, Canada).

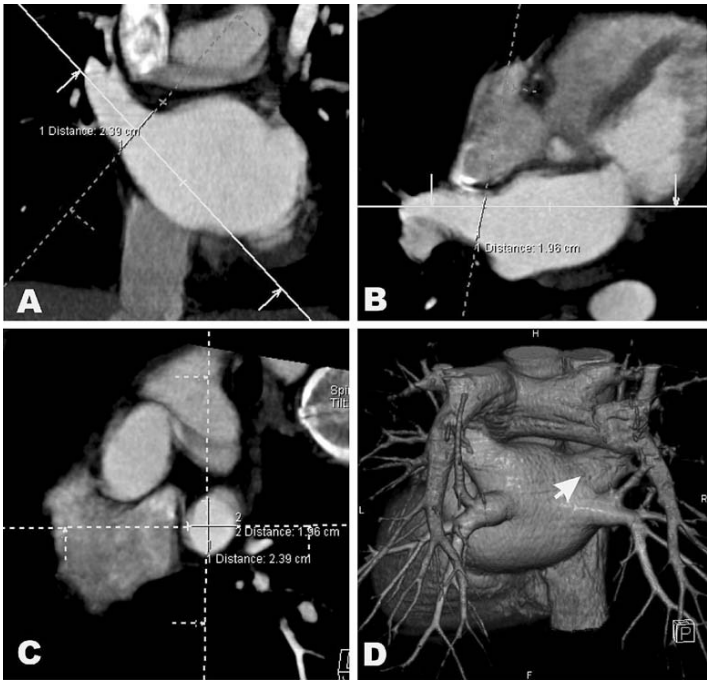

Fig. 1 Multidetector row computed tomography (*MDCT*) of pulmonary veins (*PVs*) before the ablation. **a** Coronal, **b** sagittal and **c** axial projections of the right superior PV ostium. **d** Volume-rendering (*VR*) technique, posteroanterior projection (the *arrow* indicates the right superior PV)

The cryocatheter was positioned inside the target PV under fluoroscopy guidance and by using information from intracardiac electrograms and venography. At each treatment site, CA was applied twice for 3 min with recovery to approximately body temperature between each application. If no effect was seen in the first 45 s, the catheter was repositioned and CA was repeated until all targeted PV potentials were isolated. The average freeze time duration was 59±21 min per vein (range 21–120 min), while the average duration of the whole procedure was 5±2 h per patient (range 2–6 h). The mean temperature for all ablations was −65±21°C (−39 to −65°C).

MDCT of PVs

MDCT of PVs was performed using a 16 multidetector row scanner (Sensation 16, Siemens, Germany), 1 day before and 3 months after CA. The scan range was from the aortic arch to the lower margin of the heart (range 140–180 mm), imaged during a single 3–4 s breath-hold, without ECG-gating. A bolus of 60 ml nonionic contrast material (iodixanol, 320 mg l/ml Visipaque, Amersham Health, UK) was injected into the cubital vein using a power injector set at 3 ml/s. Whenever the signal density level in the ascending aorta, which was monitored every 1.25 s, reached a predefined threshold of +100 HU above the baseline, the patient was automatically instructed to maintain an inspiratory breath-hold during which the MDCT data were acquired. The scan parameters were: detector collimation 16×1.5 mm, table feed 48 mm/s, 120 kV, 120–140 mA s (depending on the patient size), rotation time 500 ms, and estimated radiation exposure between 3.1 and 4.1 mSv [11]. Axial images were reconstructed with the following parameters: effective slice width 2 mm, increment of reconstruction 1 mm, field of view 250 mm, convolution algorithm medium.

MDCT image analysis

MDCT images from the preprocedural and postprocedural examinations were reviewed in random order by two experienced independent observers who were unaware of the patient's identity and the site of the performed ablation. Using the original data set, each investigator reconstructed

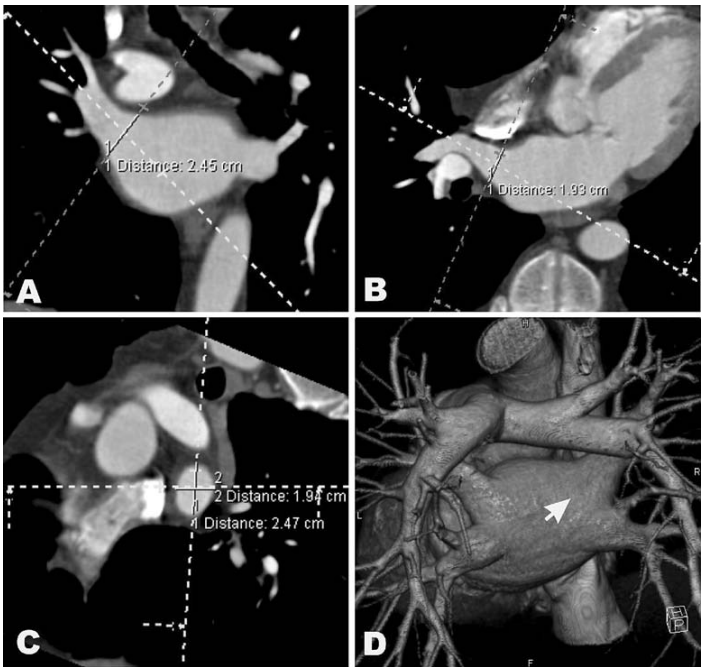

Fig. 2 MDCT of PVs in the same patient 3 months after the ablation. **a** Coronal, **b** sagittal and **c** axial projections. **d** VR technique; the posteroanterior projection shows unchanged morphology of the right superior PV (*arrow*)

images with a maximum intensity projection algorithm in three projections. Since there is no exact and clear transition from the PV to the left atrium, the PV ostium was defined as the intersection of tangents of the PV in oblique coronal projection with cranial and caudal rotation and the adjacent wall of the left atrium (Figs. 1a–c, 2a–c). Each PV was visualized in multiple projections to determine whether there was any focal narrowing. Since CA could be applied in different radial angles within the orifice circumference of the PV, both diameters were measured and the ratio was calculated and compared before and after the procedure. If only one diameter is measured in the coronal plane, a possible diameter reduction on the posterior wall of the treated vessel would be missed. Additionally, the proximal 10 mm from the ostium of the treated PV was assessed in the coronal plain given that the shape of the vessel at this distance is rounded rather then oval. A three-dimensional volume-rendering (VR) algorithm was used to evaluate the anatomical relationships between PVs, and PVs and the left atrium, which are important parameters for the mapping and further CA procedures. Surrounding structures, like aorta, vertebra, ribs, lung parenchyma and peripheral pulmonary arteries, were excluded from the display.

Statistical analysis

Categorical variables (number of treated PVs) were presented as frequencies. Continuous variables (PV diameters, ratio of PV diameters) were described by the mean ±SD, while differences among them during the follow-up period were assessed using a paired Student's *t* test at the 95% confidence level.

Results

CA was performed on 46 (47.9%) out of 96 vessels. Two PVs were treated in 21 patients, one vessel in two patients and three vessels in one patient. The left superior PV was treated in 52.2% of all the PVs, the left inferior PV in 6.5%, and the right superior PV in 41.3% (Table 1). In this study, CA was not performed in the right inferior PV. The treatment was painless in all patients, and the effective electrical isolation of PVs from the left atrium during the first ablation procedure was achieved in 37 of 46 PVs (80%) and was repeated in four patients.

Table 1 Multidetector row computed tomography measurements of the treated pulmonary veins at the ostium

Pulmonary vein	Before CA	After CA	*p*
Coronal diameter			
Left superior (*n*=24)	19.2±2.6 mm	18.3±2.2 mm	>0.05
Left inferior (*n*=3)	17.3±0.6 mm	16.7±2.3 mm	>0.05
Right superior (*n*=19)	19.2±2.2 mm	19.4±2.4 mm	>0.05
Right inferior (*n*=0)	–	–	–
Ratio			
Left superior	1.2±0.2	1.2±0.2	>0.05
Left inferior	1.1±0.1	1.2±0.4	>0.05
Right superior	1.1±0.1	1.2±0.2	>0.05
Right inferior	–	–	–

CA cryothermal ablation

Table 2 Diameters of the pulmonary veins 10 mm distal from the ostium

Pulmonary vein	Before CA (mm)	After CA (mm)	*p*
Left superior	17.1±2.8	16.7±2.5	>0.05
Left inferior	17.0±1.0	17.3±1.5	>0.05
Right superior	16.9±2.3	16.1±1.9	>0.05
Right inferior	–	–	–

Follow-up results

During the follow-up, all the patients continued with antiarrhythmic drugs. Out of 24 patients, 13 (54%) had significant clinical improvement and a reduction in the frequency and duration of atrial fibrillation episodes. The remaining 11 (46%) had no benefit from CA. There were no thromboembolic events related to the procedure, and two patients developed a hemopericardium.

Analysis of the PVs showed no changes in any of the parameters studied. The coronal ostial diameter of all the PVs treated before CA (19.1±2.4 mm) did not change significantly 3 months after the procedure (18.6±2.4 mm; $p>0.05$) (Figs. 1, 2). Table 1 presents the diameters of PVs determined by MDCT according to their anatomical position, before and after CA.

The ratio of the diameters at the ostium of the PVs before the ablation, 1.2±0.2, did not differ significantly after 3 months, 1.2±0.1 ($p>0.05$). There was no statistically significant difference in the PV ratio after 3 months in any of the treated vessels, indicating no changes in any of the diameters measured (Table 1).

Also, the PV diameter 10 mm distal from the ostium before CA, 17.1±2.5 mm, was not reduced after the procedure (16.5±2.2 mm, $p>0.05$; Table 2).

Discussion

The study showed improved clinical outcome in 54% of the patients. No PV stenosis was registered 3 months after CA in patients with paroxysmal atrial fibrillation as measured with MDCT. In none of the 46 treated PVs we found a significant diameter reduction after 3-months' follow-up. Also, there was no significant difference in the ratio of the PV diameters, which indicated no reduction in the axial

diameter (anterior or posterior sections of the treated vessels). In the first 10 mm of the veins, where ablation lesions can be found, no change in diameter was seen during the follow-up.

The clinical outcome is comparable with that of the study of Wong et al. [7], where 17/30 (57%) patients were free from atrial fibrillation or showed improvement from previously ineffective antiarrhythmic drug therapy. In contrast, in the study of Tse et al. [8], 37/52 (71%) patients had adequate control of their arrhythmia after the CA, which may be due to a different study population, the different cryoablation system used, or different cryoablation protocols [7]. Similar to our study, neither in the study of Wong et al. [7] with 47 treated PVs nor in the study of Tse et al. [8] with 152 treated veins were there stenosis during the follow-up period.

The findings on PVs corroborate with histological findings in a dog model. Feld et al. [12] reported no significant diameter reduction after extensive CA within 27 PVs in ten dogs during the mean follow-up period of 4 months. It has been hypothesized that CA preserves the basic underlying tissue architecture, produces less risk of thrombus formation [13] and therefore is expected to be associated with lower or minimal incidence of PV stenosis during the follow-up period.

In this study, CA was performed in 24 left superior and in 19 right superior PVs, which is the majority of the veins treated (94.5%). Histological findings of the human PVs revealed that atrial musculature extends beyond the venoatrial junctions into the walls of the PVs to varying distances. The thickest and the longest sleeves were found in the left superior and right superior PVs [14], which could explain the high incidence of arrythmogenic foci with consequent CA in these vessels in our study.

Different imaging modalities have been used for monitoring the PV diameter after ablative treatment during long-term follow-up periods. However, by transesophageal echocardiography visualization of the lower PVs is often difficult or impossible, as described by Yu et al. [15], who reported data only for the upper PVs during and after radiofrequency catheter ablation. Contrast-enhanced three-dimensional magnetic resonance angiography has been proven to be an accurate and highly reproducible method for evaluation of congenital PV anomalies and the evaluation of the diameter of PVs before and after radiofrequency catheter ablation and therefore is a good imaging modality in patients without contraindications for magnetic resonance imaging examination [16].

Angiography using 16 MDCT has been shown to be an accurate method for visualization of PVs with good interobserver agreement and interexamination reproducibility [17]. The data set is acquired with high spatial resolution of isotropic, submillimeter voxels, and image reformats can be made off-line in any desired imaging plane and section thickness. Retrospective creation of thinner or thicker sections from the same raw data allows detailed evaluation not only of superior and inferior walls of the veins as with conventional methods, but also anterior and posterior walls and measurements of the lumen. The improved three-dimensional VR technique enables panoramic visualization of PV anatomy and assessment of the anatomical relationships of PVs, and PVs and neighboring structures, which is important information for planning a CA procedure. Although the PVs have a certain basic pattern, the incidence of variant anatomy ranges from 23 [14] to 38% [18] and is important in planning ablation and ascertaining that all PV orifices are evaluated during the procedure.

Conclusions

Although the study included 46 treated PVs, this number was shown to be sufficient for detecting even minimal changes in the vessel diameter. Also, considering the known incidence of PV stenosis in the studies on radiofrequency ablation, and the number of ablated PVs in this study, it could be reasonable to expect some PV stenosis if CA was prone to cause it.

CA in patients with atrial fibrillation appears as a promising and safe procedure with no PVs stenosis after 3-months' follow-up. Contrast-enhanced 16-slice MDCT allows quantitative assessment and good visualization of PVs in short times. The noninvasive nature of MSCT and the ability to demonstrate three-dimensional anatomy of the veins and the surrounding structures are important features for evaluation of PVs before and after the CA procedure.

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Chapter 13

Catheter ablation of atrial fibrillation; still investigational or already an esthablished therapy?

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Europace 2004;9:79-81

Catheter ablation of atrial fibrillation: still investigational or already an established therapy?

The multiple wavelet theory of Moe [1], later supported by animal studies [2], explaining that atrial fibrillation (AF) can only become established when more than a critical number of wavefronts coexist in the atrium, was a major step in our understanding of this complex and multifactorial disease. This concept is one of the cornerstones leading to the development of a successful antiarrhythmic approach to interrupt conduction in both atria, by creating a network of surgical lines, similar to a maze [3]. However, catheter-based maze procedures (in comparison with the surgical procedure), lacked efficacy and were associated with major complications such as stroke and pericardial effusion [4].

The treatment of atrial fibrillation entered a new era after the publication of the landmark observations of Haïssaguerre et al. [5]. The recognition of the role of myocardial extensions [6] within the pulmonary veins in initiating AF changed both pathophysiological insights and the therapeutic approach. For the first time it was expected that electrophysiologists could cure AF the way they could cure patients with accessory pathways, atrial flutter and AV nodal re-entrant tachycardias. As usual, the initial enthusiasm was followed by the awareness of limitations. Nevertheless, the approach of pulmonary vein (PV) ablation has stayed on the agenda.

Myocardial sleeves

It has been known for some years that the left atrial myocardium extends a few centimetres into the pulmonary veins [6]. Embryological studies explained their possible role in arrhythmogenesis [7]. While this might explain the pacemaker activity in these fibres, it is not clear why this ectopic activity triggers AF in a limited number of people (''what triggers the trigger?''). The paper in this issue by De Ponti and co-workers [8], showing that one third of the patients has this kind of ectopic activity in the PVs elegantly demonstrates the potential of high-density mapping using a multi-electrode basket catheter in clarifying conduction and breakthrough patterns. Longitudinal conduction in the PVs is helpful in understanding activation patterns and finding ablation sites [9]. Electrode systems such as the basket have therefore a role in helping us to understand the physiology of a PV, and are probably more helpful in this respect than semicircular or circular electrode catheters, which can only show one level of abnormal electrical activity.

Success rate

The long-term effect of PV ablation is not known despite the high initial success rates that have been reported [10,11]. It has become clear, however, that a high percentage of patients experience recurrences [12]. This raises questions about the value of the procedure. Overestimation of the possible results to be achieved is now replaced by redefined expected ablation endpoints. Complete isolation of all veins remains the best option—return of conduction will nevertheless occur in a certain number.

Diagnostic issues

Persistent triggering can be due to the existence of extrapulmonary vein foci (vena cava, left atrium). Better than hunting for ectopic activity might be segmental ostial catheter ablation [13] or left atrial encircling ablation of the PVs [10]. That methods to improve the ablative diagnostic approach exist is demonstrated by one paper in this issue, illustrating how inventively generally

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doi:10.1016/j.eupc.2003.12.001

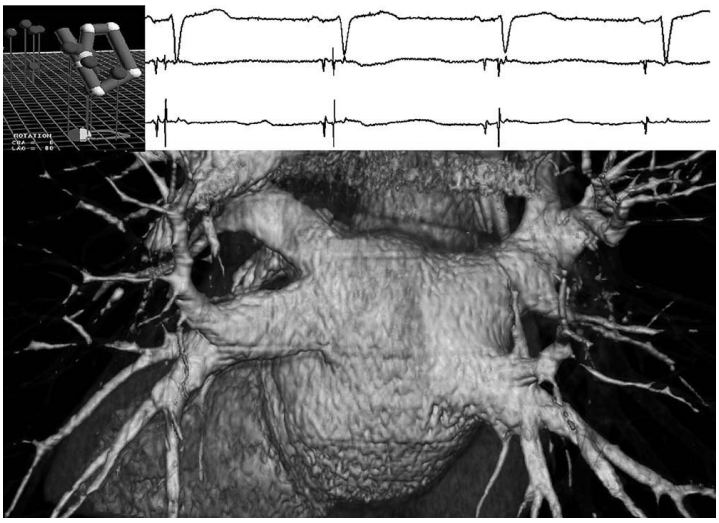

Figure 1 Cornerstones of modern pulmonary vein ablation for atrial fibrillation. A (left upper corner): image obtained with LocaLisa illustrating a level within a pulmonary vein, to guide ablation (red dots). B (right upper corner): disappearing pulmonary vein potential during catheter ablation (surface electrocardiogram and two intracardiac electrograms). In the first two complexes an atrial potential is followed by a pulmonary vein potential. This spike starts dissociation in complex 3, and disappears in complex 4. C (lower picture): dorsal view of reconstructed left atrium and pulmonary veins with 16 row spiral computerised tomography.

available tools (Fig. 1) can be adapted to isolate pulmonary veins [14]. Intracardiac echocardiography is a more powerful diagnostic tool than pure navigation mapping, and can help to understand (normal or abnormal) anatomy and, moreover, has now been reported as a guide for RF ablation [15].

Therapeutic options

The best energy source for ablation is still a matter of debate; conventional radiofrequency is associated with serious complications [16]. The ''How to…'' paper by Gill, included in this issue, describes how to avoid such complications. The author uses a conventional energy source and is avoiding applications in the vein [17]. The irrigated tip probably causes less problems and is more effective [18]. New energy sources such as cryothermy [18,19] or ultrasound [20] are promising. New catheter systems should be developed to optimise therapy delivery [21]. The so-called ''left isthmus line (from left inferior PV to mitral annulus)'' may be an important addition to PV isolation.

Complications

Paralleled by the number of procedures, the knowledge of possible complications has increased. Known complications include pulmonary vein stenosis, thromboembolism, haemopericardium and damage to adjacent structures such as pulmonary artery, phrenic nerve and lung tissue. In this issue Schwab et al. describe the occurrence of temporary ST elevation and elevation of troponin readings [22]. They hypothesize that this resulted from catheter induced coronary spasm while moving in the dorsal part of the left atrium. However, such abnormalities are not uncommon [19].

Mansour and colleagues observed early formation of a left atrial clot using intracardiac echocardiography [23]. Their observations are important and support the policy of rapid and adequate anti-coagulation with heparin after (or before?) transseptal puncture. An anti-coagulation policy put forward in the Gill ''How to…'' article in this issue is one approach. However, this should be adapted to local habits and control, until more evidence-based data are available [17]. Transoesophageal echo is part of the protocol in some institutions, and can be helpful in preventing

stroke [15]. The incidence of pulmonary vein stenosis is another important outcome variable and its development in long-term follow-up is not known. Comparison of the reported frequency of PV stenosis after ablation is difficult because of the different diagnostic modalities (angiography, CT and MRI) used. Its occurrence stimulates the search for alternative energy sources for ablation. In our and others experience [19,20], cryothermy ablation is promising in this respect.

Patient selection

Important is the selection of patients who will most likely profit from PV ablation [17]. Possibly, the need for different procedures depends on the relative importance of substrate and triggers in a given patient [24]. The improvement in quality of life found [12] in patients who were ablated but with recurrences of AF is not explained, but may result from altering left atrial innervation.

Future directions

Atrial fibrillation is an arrhythmia with a multifactorial aetiology. It is very unlikely that a single solution for all AF patients will be developed. The role of increasing fibrosis is probably of the utmost importance in the elderly, in patients with hypertension and in those with valvular heart disease. Therefore, attention should be directed towards drugs that prevent or diminish fibrosis and at ablation procedures targeting the substrate. For a subset of patients, PV ablation therapy, today, is a promising alternative to unsuccessful drug therapy. Investigational modalities of energy delivery seem to be important, in order to avoid complications. Further technological improvement such as a magnetic navigation system [25,26] can potentially be of help in mimicking the surgical maze procedure by a catheter-based approach, which should result in similar efficacy. One thing is evident: many strategic and practical questions need to be answered before this approach is to be considered an established therapy.

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Chapter 14

Pulmonary vein antrum isolation guided by phased array intracardiac echocardiography, a third way in AF ablation

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Netherlands Heart J 2005;12: 439-443

Pulmonary vein antrum isolation guided by phased-array intracardiac echocardiography

A third way to do PV ablation

M.F. Scholten, A.S. Thornton, J. Mekel, M.J. Rivero-Ayerza, N.F. Marrouche, L.J. Jordaens

Background. **Pulmonary vein isolation (PVI) has emerged as an important strategy in the treatment of patients with atrial fibrillation (AF).The two most frequently used techniques are segmental PVI and left atrial circumferential ablation.**
Aim. **To describe and discuss pulmonary vein antrum isolation guided by phased-array intracardiac echocardiography (ICE) as an alternative approach, and to present initial results.**
Methods. **Patients with symptomatic AF were included. The antra (the larger circumferential area around the PVs) were isolated guided by ICE. ICE was also used to titrate the ablation energy.**
Results. **38 patients (3 with persistent AF) were included. Of the 35 patients with paroxysmal AF, 24 are without recurrences, and in six the incidence of paroxysms was significantly reduced after one procedure and a mean follow-up of 201 days. No major complications occurred.**
Conclusion. **Pulmonary vein antrum isolation guided by ICE is a promising technique in AF ablation and has the potential to avoid severe complications. (*Neth Heart J 2005*;13:439-43).**

Keywords: atrial fibrillation, PV isolation, intracardiac echocardiography

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Isolation of the pulmonary veins (PVI) has emerged as an important strategy in the treatment of patients with atrial fibrillation (AF). Several studies have demonstrated freedom from AF after complete PVI in 70% of patients presenting with paroxysmal AF.[1-3] In this paper we describe an intracardiac echocardiographically guided technique for PVI and report the initial results and complications of an ongoing study using this method, aiming at ablation of the antrum (the larger circumferential area around the PVs) rather than at the PV itself, to improve outcome and to prevent the occurrence of potentially serious complications.

Methods

Inclusion criteria

Patients with symptomatic paroxysmal AF despite at least two antiarrhythmic drugs, in the absence of significant heart disease, were included in an ongoing prospective clinical trial. Initially, patients with persistent AF could be included as well. Additional inclusion criteria were a left atrial dimension <55 mm, willingness to comply with invasive screening and follow-up procedures, and the absence of echocardiographic abnormalities during transoesophageal echocardiography (TOE) the day before the procedure. A multislice CT scan was performed to assess the anatomy and measure the diameter of the PVs.

Ablation procedure

A general outline of this procedure has already been given elsewhere.[4,5] A 10 Fr intracardiac echocardiography (ICE) catheter (Acunav, Siemens AG Inc., Malvern, PA, USA) is introduced through the left femoral vein and positioned in the right atrium. The subclavian vein is used to advance a decapolar stimulation catheter into the coronary sinus. Two long sheaths are advanced through the right femoral vein into the right atrium. Double transseptal puncture is carried out using a Brockenbrough needle guided by both ICE and fluoroscopy. ICE is also used to ensure a posterior transseptal approach. A circular mapping catheter is advanced and positioned in the antrum of the pulmonary veins (figure 1).

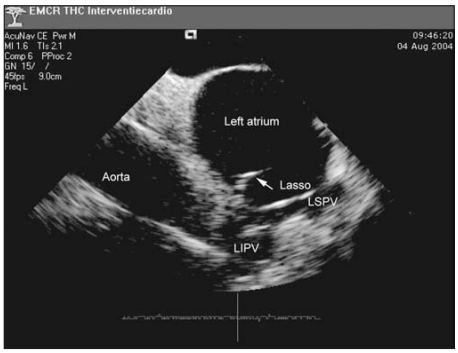

Figure 1. Phased-array intracardiac echocardiogram: circular multipolar catheter (Lasso) in the antrum of the left inferior pulmonary vein. LIPV=left inferior pulmonary vein, LSPV=left superior pulmonary vein.

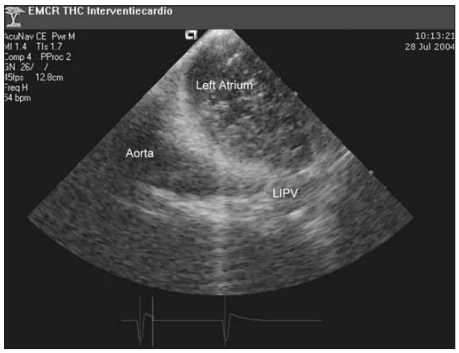

Figure 2. Phased-array intracardiac echocardiogram: microbubble formation during ablation, caused by overheating of the tissue, showing a 'brisk shower' and ablation is stopped immediately.

Radiofrequency energy is delivered using an 8 mm ablation catheter aiming at abolishing all PV potentials registered with the roving circular mapping catheter. RF energy is set at 30 Watts and 55°C and increased by 5-Watt steps to a maximum of 70 Watts or until microbubble formation (figure 2) occurs.

After isolation of all four PV antra the circular mapping catheter is placed in the superior caval vein (SVC) and this vein is also isolated. Ablation in the SVC is only carried out if there is no phrenic nerve stimulation while pacing at a high output in this vein. The day after the procedure a transthoracic echocardiogram is preformed to exclude pericardial effusion.

Anticoagulation protocol

All patients are treated with the coumadin preparation acenocoumarol for at least one month before the procedure, aiming at an INR of 2.5 to 3.5. Two days before the procedure, patients are admitted to hospital and the acenocoumarol is replaced by unfractionated heparin, aiming at an APTT ratio of three times the normal. A transoesophageal echocardiogram (TOE) is carried out the day before the ablation to exclude atrial thrombi. Two hours before the ablation, the heparin is stopped. After venous puncture and before transseptal puncture a 5000 E heparin bolus is given. After successful transseptal puncture another 5000 E heparin is given and a continuous titrated infusion of heparin is started. During the procedure the activated clotting time (ACT) is monitored every 30 minutes and is kept above 350 msec with bolus doses of heparin and adjustment of the infusion rate. After the procedure the patients are treated with heparin, and acenocoumarol is restarted. Heparin is stopped when the INR is above 2.5. Acenocoumarol is continued for at least six months.

Antiarrhythmic drug treatment after ablation

During the first two months after ablation all patients are treated with flecainide and bisoprolol to suppress atrial ectopy caused by the ablation. These drugs are stopped after two months if AF does not reoccur.

Follow-up methods

All patients are followed intensively in the outpatient clinic, including daily transtelephonic ECG monitoring from one month before until three months after ablation. Multislice CT scans are repeated at three months to evaluate the possible occurrence of PV stenosis, defined as a reduction in the diameter of more than 80%.[6]

Results

Patients

A total number of 38 patients (6 females), mean age 50.7 years (23 to 68 years), were included. Three of these patients had had persistent atrial fibrillation for more than one year and had to be cardioverted into sinus rhythm before ablation. Seven patients had previously undergone a right atrial isthmus ablation for atrial flutter. The mean LA dimension, as measured with transthoracic echocardiography, was 44.6 mm (32-53 mm). One patient had a fifth pulmonary vein on the right side. As the antra of the pulmonary veins often merge at the level of the atrium, this often creates the impression that there is a common origin of unilateral PVs.

Procedure and complications

All transseptal punctures were uneventful. In the first 38 patients, 150 pulmonary veins could be electrically isolated. All PVs were isolated in 36 patients. The

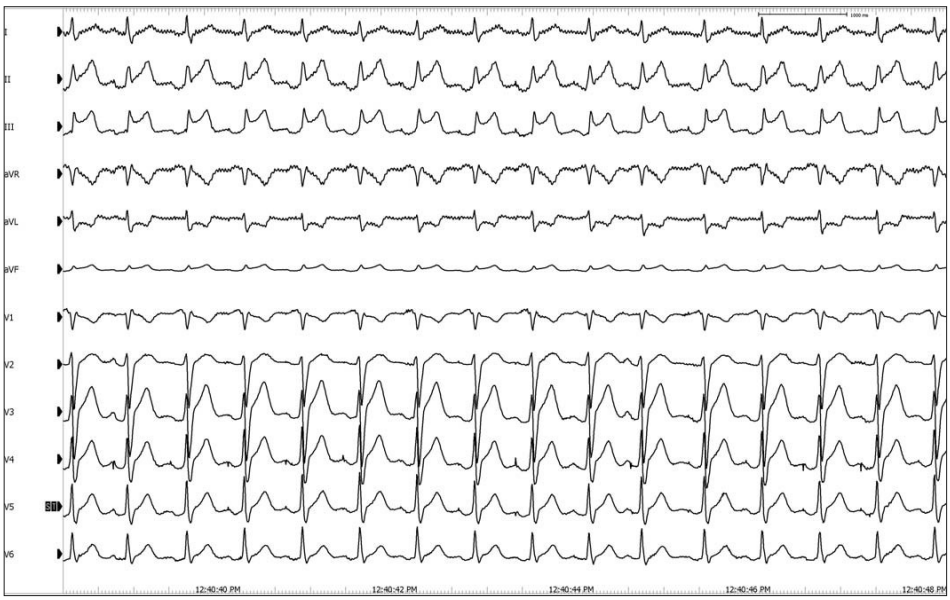

Figure 3. Transient ST elevation in the inferior leads after transseptal puncture.

average procedural time was 229 minutes (145-396) and the average fluoroscopy time 94 minutes (52-147). The average radiofrequency application time was 4098 seconds (1569-7999). The three patients with persistent AF were cardioverted several times during the ablation procedure. Of the other 35 patients, 17 were cardioverted once or twice during the procedure. In two patients, asymptomatic and transient ST elevation (figure 3) was observed after transseptal puncture.[7]

No echocardiographic evidence of myocardial infarction was observed. In four patients a right-sided isthmus ablation was carried out during the same procedure. In nine patients the superior caval vein (SVC) was isolated as well. This was not done in those patients undergoing phrenic stimulation during pacing in the SVC. In one patient an asymptomatic hemidiaphragmatic paralysis was seen immediately after ablation. No other complications occurred, except for two vagal reactions.

Follow-up

Mean follow-up in the described patients is 201 days (SD 10 days, 1-360 days). PV stenosis was not seen. Only one of the three patients with persistent AF was in sinus rhythm after the procedure. All three patients now have permanent AF. AF recurrences were seen in 11 of the 35 patients with paroxysmal AF. In six of these 11 patients the incidence of AF paroxysms was significantly reduced. AF was recorded in 34.6% of transmitted ECG strips before and 6.4% of transmitted ECG strips after PVI. Two patients developed a symptomatic atrial flutter, and were treated successfully with right-sided isthmus ablation.

Discussion

The first successful nonpharmacological treatment for AF, aiming at changing the substrate, was the Maze procedure.[8] Stimulated by the success of this procedure, initial ablation attempts were made to copy the Maze procedure, using transvenous ablation. The idea was to compartmentalise both atria by making long linear lesions. These procedures, however, were not successful because of technical difficulties in creating linear lesions, morbidity associated with this approach, long duration of the procedure and moderate effect on AF burden.[9] Two strategies for PV isolation emerged as more effective, and became major therapeutic options for patients with paroxysmal AF.

Classical techniques in radiofrequency AF ablation

Haissaquerre et al. drew attention to the role of focal activity within the pulmonary veins in triggering and maintaining AF.[10,11] Based on this knowledge he

originally performed radiofrequency (RF) ablations only at sites within the PVs where ectopic activity was recorded.[10] It is now accepted that the results of ablation improve if all PVs are completely isolated from the left atrium. Because the risk of PV stenosis with RF energy was substantial, ablation is now targeted at the ostia of the PVs. The endpoint of this approach (often referred to as the Haissaquerre approach or segmental PVI) is the elimination of all ostial PV potentials and the demonstration of complete entrance block. In this technique the ostium of the PVs is assessed by angiography.

Another successful approach in AF ablation, originally designed to isolate the PVs with a reduction in the risk of PV stenosis, is the circumferential pulmonary vein ablation.[3] This technique, developed by Pappone et al., is also known as left atrial radiofrequency circumferential ablation (LACA). Continuous circular lesions are made around each PV or around ipsilateral PVs with the help of a virtual three-dimensional (3D) electroanatomical mapping system. The ostium of the PVs is identified by fluoroscopy and during withdrawal of the catheter from the PV, with a simultaneous impedance decrease and appearance of atrial potentials. The endpoint of this approach is a low peak-to-peak bipolar potential (<0.1 mV) inside the circular lesion. The results of LACA are better when complete PV isolation, which can be considered to be a hybrid endpoint, is reached.[12]

Possible complications of PVI

Several complications of PVI have been reported. Severe thromboembolic complications are possible[13] and therefore good anticoagulation is warranted. PV stenosis has gained a lot of attention.[14] The incidence seems to decline with growing experience and with more proximal ablation.

Perforation, pericardial effusion and even tamponade have been described.[15] The left atrial appendage (LAA) is especially vulnerable to perforation and should be avoided during ablation. PVI can cause the appearance of new arrhythmias,[16,17] such as atrial tachycardia and left atrial flutter. The most feared complication nowadays is perforation at the posterior wall and the subsequent development of a left atrial-oesophageal fistula.[18-21]

Rationale for using intracardiac echocardiography

Intracardiac echocardiography (ICE) enables transseptal puncture and makes it safer.[22] Because ablation should target the ostia of the PVs, imaging of the pulmonary veins during the procedure is important. Angiography shows only the tunnel-shaped portion of the PVs, while in reality the PV antrum is more funnel-shaped, as can be seen on 3D multislice CT scan reconstructions (figure 4).

Real-time imaging of the PV antrum is currently only possible with ICE. Overheating of the tissue carries a risk of perforation and thrombus formation. Microbubble formation is a good indicator of excessive temperature and steam formation.[23] Monitoring microbubble formation with ICE can therefore be used to prevent overheating.[24] Ablation within the thin-walled LAA is prevented by the visualisation of this structure. ICE is the only tool available today to provide us with real-time imaging, making it possible to ablate in the antrum of the PVs and to ensure good wall contact. The use of ICE also holds promise for reducing fluoroscopy time; the fact that we could not demonstrate this is partly due to the learning curve involved in this technique. The average fluoroscopy time in more recent cases in our clinic has fallen below 60 minutes.

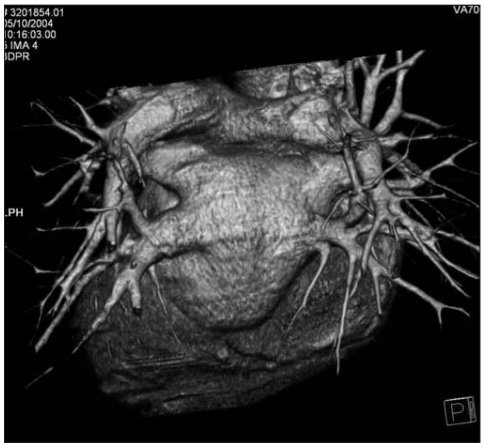

Figure 4. 3D reconstruction multislice CT scan. Posterior view. The tube-shaped portion of the pulmonary veins becomes funnel-shaped before entering the left atrium.

Merging techniques to improve efficacy and reduce complications

The differences between the two most frequently used techniques (segmental PVI vs. left atrial circumferential ablation) (figure 5) have often been passionately discussed. Pioneering groups using the segmental PVI reported freedom of AF without antiarrhythmic drugs in 70% of patients presented with paroxysmal AF.[25,26] This success rate was definitively lower compared with the LACA approach of Pappone et al.[3] reporting freedom of AF in 85% of patients. This was attributed to the reduction of electrically active tissue (substrate) with the wide encircling lesions. This difference between the two techniques disappears, however, with the more proximal ablation used today by those performing segmental ablation and with the complete PV isolation achieved with LACA. The electroanatomical mapping used in left atrial circumferential ablation has advantages because it creates a 3D map

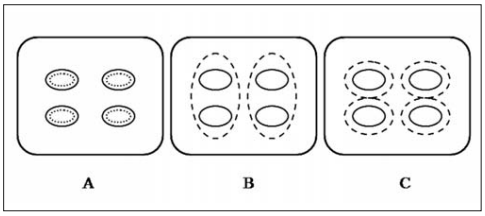

Figure 5. Schematic representation of the three described techniques. The PVs are drawn as four circles and the ablation lesions as dotted lines. A. Ostial PV isolation originally described by Haissaquerre et al. B. Circumferential ablation first described by Pappone et al. C. Typical lesions set after intracardiac echo-guided PV isolation.

enabling navigation. However, this 3D environment is virtual and often does not account for the funnel shape of the proximal part of the PV. The reported clinical results of the ICE-guided antrum ablation are very good, even in patients with structural heart disease.[27] The initial results of our ongoing experience are very promising. Despite the growing experience with the procedure and the improvement in success rate, PVI remains an invasive procedure and major and sometimes life-threatening complications can occur. We strongly believe that pulmonary vein antrum ablation guided by ICE has the potential to avoid several complications because it uniquely provides online visualisation of the left atrium together with the possibility to titrate energy in order to prevent overheating. This results in less PV stenosis and seems promising to avoid left atrial oesophageal fistulae. ■

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Chapter 15

Comprehensive follow-up after antral pulmonary vein isolation in patients with paroxysmal atrial fibrillation

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submitted

COMPREHENSIVE FOLLOW UP AFTER ANTRAL PULMONARY VEIN ISOLATION IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

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ABSTRACT

Introduction Isolation of the antrum of the pulmonary veins (PVI) is a recent invasive strategy for the treatment of atrial fibrillation (AF). Assessment of its success depends on the intensity of follow-up methods and the definitions used.
Aim To analyse success rate and recurrences using a symptom score, Holter ECG and event monitoring.
Methods Patients with symptomatic AF were treated with echocardiographically guided antral PVI and prospectively followed. Before and 3 months after ablation, a symptom score and a 24 hours Holter-ECG were obtained. AF, atrial arrhythmia, and symptom burdens were assessed with daily transtelephonic ECG monitoring, from one month before to 3 months afterward ablation.
Results 41 patients (7 females), mean age 52 years (24-72 year), with a mean LA dimension of 43 mm (32-53 mm) completed at least 3 months follow-up. Four patients developed a more permanent pattern in the weeks before PVI. The symptom score list assessed duration and intensity. Using 24 hours Holter-ECG, AF was recorded in 22/37 patients (59%) before ablation, of whom 7 had continuous AF. AF burden (defined as % of days with AF on event recording) was 37%, and events occurred in 32/39 (82%) patients. Atrial arrhythmia (AA) burden was 40%, symptom burden (% days with symptomatic events) 27%. In total, 162 pulmonary veins were isolated. Symptom scores changed significantly with respect to frequency and duration. AF was seen on Holter in only 5/40 patients after 3 months (13%) ($p < 0.001$) Three out of 4 permanent AF patients kept incessant AF. AF recurrences were seen in 20/41 patients using event monitors ($p<0.02$). In 8 of these 20 patients only one or two episodes of AF were recorded. At months 1, 2 and 3, AF burden became 12; 10 and 12%, AA burden became 16; 14 and 18%, and symptom burden 14; 9 and 9 %. Differences were highly significant between pre-ablation and all 3 follow-up months for AF, AA and symptom burden ($p <0.005$).
Conclusion The clinical improvement after antral PVI was highly significant. Daily transtelephonic monitoring reveals more accurate information on arrhythmia recurrences than Holter- ECG alone. Other arrhythmias interfere with the perception of clinical success. A significant number of AF episodes are asymptomatic.

KEY WORDS

arrhythmia; atrial fibrillation; catheter ablation; Holter recording; intracardiac echocardiography; pulmonary vein isolation

INTRODUCTION

Isolation of the pulmonary veins (PVI) has emerged as an important strategy in the treatment of patients with atrial fibrillation (AF). Several studies demonstrated freedom from AF after complete PVI in 70% of the patients with paroxysmal AF(1-3). A large variability in success rates between different groups was found in a world wide survey(4). This is partly dependent on growing experience, and probably on definitions used for success and follow-up methods. The success rates for patients with persistent AF are lower, probably because mechanisms other than initiating triggers play an important role. The methods used for follow-up after PVI are important in assessing the true incidence of recurrences and the reported success rate, because of the possibility of asymptomatic periods of AF(5). The incidence of asymptomatic periods of AF after successful PVI is supposed to be low(6). However, using implantable loop recorders, others have found an incidence of asymptomatic AF periods of 38% in a similar group (7). The aim of this study is to describe, with a comprehensive and intensive follow up method, using a symptom score, Holter-ECG and event monitoring, the results of antral PVI for patients with paroxysmal AF.

METHODS

Patients

Patients with paroxysmal AF despite at least two anti arrhythmic drugs were accepted as candidates for antral PVI. Exclusion criteria were: left atrial dimension > 50 mm measured in the parasternal long axis as assessed with transthoracic echocardiography, structural heart disease and advanced age.

Ablation procedure

All patients were treated with intracardiac echocardiographically (ICE) guided antral PVI (8). Both femoral veins and the left subclavian vein were used for venous access. A 10 Fr, 64 element phased-array ICE catheter (Siemens AG inc., Malvern, PA, USA) was introduced through the left femoral vein and positioned in the right atrium. The subclavian vein was used to advance a decapolar stimulation catheter into the coronary sinus. Double transseptal puncture was performed using a Brockenbrough needle and guided by both ICE and fluoroscopy. ICE was also used to ensure a posterior transseptal approach. A circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) was advanced and positioned in the antrum of the pulmonary veins. Radiofrequency energy was delivered using an 8 mm ablation catheter (Blazer 8 mm, Boston Scientific, Natick, MA, USA) aiming at abolishing

all pulmonary vein potentials registered with the roving circular mapping catheter. Ablation energy was titrated under ICE guidance between 30 and 70 Watts, based on micro bubble formation(9). After isolation of all 4 antra the circular mapping catheter was placed in the superior caval vein (SVC) and this vein was also isolated unless phrenic nerve stimulation occurred while pacing at a high output in this vein. If clinically indicated, an additional ablation of the cavotricuspid isthmus was performed. The day after the procedure a transthoracic echocardiogram was made to exclude pericardial effusion, and a chest X-ray to exclude pneumothorax and other thoracic complications.

Anticoagulation

All patients were treated with coumadine derivatives for at least one month before the procedure aiming at an INR of 2.5-3.5. Two days before the procedure patients were admitted and the oral anticoagulants were replaced by unfractionated heparin, aiming at a PTT ratio 3 times normal. Two hours before the ablation heparin was stopped. After venous puncture and before transseptal puncture a 5000 IU Heparin bolus was given. After transseptal puncture another 5000 IU Heparin was given and a continuous titrated infusion of heparin was started. During the procedure the activated clotting time ACT was monitored every 30 minutes and was kept above 350 s with additional doses of heparin and adjustment of the infusion rate. After the procedure the patients were treated with heparin and oral anticoagulants were restarted. Heparin was stopped when the INR was above 2.5 on 2 consecutive days. Oral anticoagulation was continued.

Anti-arrhythmic drug treatment after ablation

During the first two months after ablation all patients were treated, if possible, with flecainide and bisoprolol. These drugs were stopped after two months if there was no recurrence.

Follow up methods

Before ablation a symptom score list was completed, to classify duration and frequency in a standardized way.

The Holter-ECG was also used to calculate average heart rate in sinus rhythm. Sustained AF on the Holter was defined as AF periods of at least 30 seconds. When AF persisted, the mean AF rate was calculated. Atrial premature contractions (APC`s) and atrial runs were counted.

The symptom score list and the Holter-ECG were repeated after 3 months. Patients were instructed to use an event recorder and to transmit daily at least one transtelephonic ECG-strip at a fixed hour, and when symptoms were present. This was

started one month before ablation and continued for three months afterwards. The heart rhythm on the ECG-strips was coded as sinus rhythm, atrial flutter, atrial tachycardia or atrial fibrillation. Atrial and ventricular premature beats and sinus tachycardia were coded, but are not reported, as they were infrequent. For analysis, atrial tachycardia and flutter were pooled, as discrimination between both arrhythmias was often impossible. Transmissions were coded as symptomatic or asymptomatic. The AF burden was defined as the percentage of days on which an AF episode was transmitted. A combined atrial arrhythmia burden of AF, atrial flutter and tachycardia was calculated. Symptom burden was defined as the percentage of days when symptomatic episodes were transmitted.
Multislice CT scans were made before and at 3 months after ablation to evaluate the possible occurrence of PV stenosis as described before(10). PV stenosis was defined as a reduction of the diameter of more than 25%. Patients were seen at the outpatient clinic after 6 weeks and at 3 months when they returned the event recorder.

Statistical analysis

Continuous variables are expressed as the mean value ± SD and were compared with the t-test. A chi-square test was used for categorical variables. Symptom scores were analyzed with a Wilcoxon rank test.

RESULTS

Patient data

A total number of 41 patients (34 male, 7 female), mean age 52 years (24-72 year), completed at least 3 months follow up in this prospective study. Four patients were previously classified as having paroxysmal AF, but had developed a more continuous pattern in the weeks before the procedure (they will be referred to as incessant). The mean LA dimension was 43±5 mm (32-53 mm). Thyroid disorders had been diagnosed in 6; hypertension was the underlying disease in 5, valvular disease was present in one patient. In 11 patients atrial flutter had been recorded before. A total number of 14 patients had been treated with amiodarone, and 29 had undergone cardioversion in the past. Cavotricuspid isthmus ablation was performed in 10 before the PVI, an accessory bypass tract was previously ablated in one patient. One patient had a pacemaker. The mean follow-up to November 11th 2005 is 332±124 days (range 86 to 519 days).

PROCEDURES

During 41 procedures, 162 pulmonary veins were isolated with an average radiofrequency application time of 70±26 minutes. The superior caval vein was isolated in 20 patients. The cavotricuspid isthmus was ablated in 5 patients in the same procedure.

The average procedure time was 225±59 min (range 128-396 min) and the average fluoroscopy time 95±27 min (range 52-147 min). Twenty patients had to be cardioverted during the procedure. In this series no severe complications requiring prolonged hospitalization occurred. Significant pericardial effusion was not seen. In one patient asymptomatic diaphragmatic paralysis was seen immediately after the procedure. It partially recovered after 3 weeks.

Symptom scores and cardioversions

At baseline the symptom frequency was reported as daily by 8 patients (20%), weekly by 22 patients (54%) and monthly by 7 patients (17%). Symptoms were permanent or incessant in 4 patients (10%), but minimal in intensity in 2 of these. The duration of symptoms was expressed in days in 2 patients (5%), in hours in 31 patients (79%) and in minutes or seconds in 2 patients (5%). All 4 incessant patients could not determine the duration of their symptoms.

At 3 months the symptom frequency was reported as daily by 4 patients (10%); weekly symptoms were present in 4 patients (10%); monthly in 5 patients (12%). Two patients only noted one episode over the 3 months (5%). Symptoms remained incessant, but minimal in intensity in 3 patients (7%). All 23 others (56%) had no more symptoms. The duration of symptoms at 3 months was expressed in days in 4 patients (%), in hours in 8 patients (17%), in minutes or seconds in 3 (7%). Three incessant patients had ongoing symptoms.

The symptom score at 3 months changed significantly for frequency ($p<0.0001$) and duration ($p <0.0001$) versus the baseline data (figure 1).

A total number of 34 (83%) patients assessed their clinical course as significantly improved with respect to symptoms; it remained equal in 3 (7%); it became worse in 4 (10%).

In the year prior to PVI 1-8 cardioversions were performed in 16 patients (39%). A total of 8 patients were cardioverted in the three months after PV ablation (range 1-3).

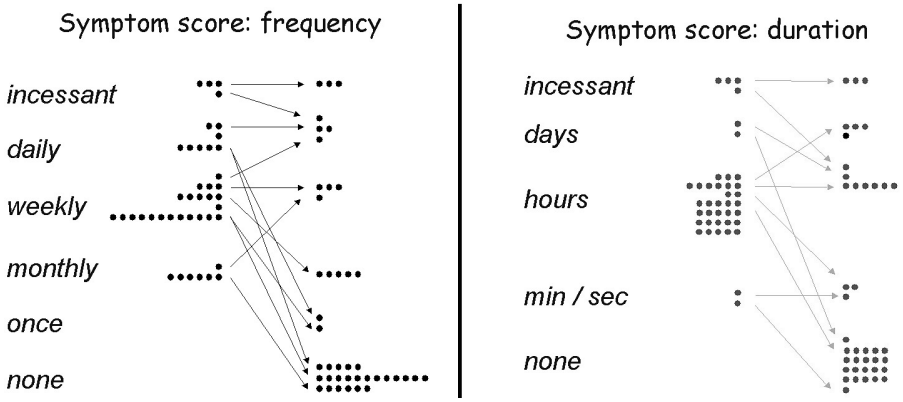

Figure 1: Symptom score before and 3 months after ablation. Each patient is represented by a dot. Shown are frequency and duration of the symptoms.

Holter ECG recordings

A Holter was not performed before the ablation in 4 patients for a number of logistic reasons. In the remaining 37 patients, the mean 24 hour heart rate was 71±12 bpm, and AF was present in 22/37 patients (59%), including (unexpectedly) continuous AF over 24 hours in 7 patients. The mean ventricular rate during AF in these patients was 83 ±18 bpm. Paroxysmal AF was present in 31±20% of the time in those with AF. The median number of APCs in the patients without continuous AF was 128 (present in all), and a median number of 6 runs of atrial tachycardia in 15 patients was observed.

In the Holter-ECG`s at 3 months, available in 40 patients, the mean 24 hour heart rate was 71±10 bpm (NS). Sustained AF was detected in 5/40 (13%) patients. AF was continuous throughout the recording in 3 of the 4 patients with the incessant AF in the first recording and in another one. The mean ventricular rate during persistent AF was 100±26 bpm ($p<0.02$). The median number of APC`s in the patients with paroxysmal AF was 62 (present in all 35 patients), and a median number of 4 runs (in 12 patients) was observed. The number of APC`s and runs was not significantly different compared with the Holter-ECG before ablation. Significantly less patients showed AF ($p<0.001$) while the number with APC`s and runs did not change.

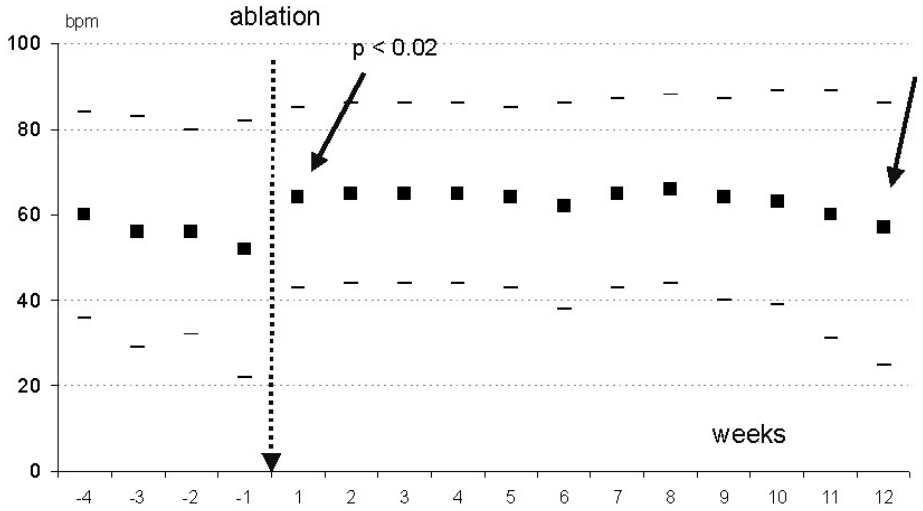

Figure 2: Average heart rate per week before ablation and in the 3 months of follow-up.

Event monitoring

All patients except 2 with incessant AF submitted rhythm strips on a daily basis before the intervention. These 2 were assigned a pre-ablation burden of 100%, but not counted in the number of analyzed rhythm strips. Before ablation 737 ECG rhythm strips were available for analysis. The average heart rate in sinus rhythm was 64±12 beats per minute in the month before ablation. Figure 2 shows the average heart rate per week. In the rhythm strips, AF was recorded 228 times (37.9%), in 32/39 patients (not including the 2 previously known incessant patients). Atrial flutter or atrial tachycardia was recorded in 40 rhythm strips (5.4% in 12 patients). AF, atrial flutter or atrial tachycardia) was observed in 33/39 patients. The AF burden (37.4%) and the combined atrial arrhythmia burden (40.2%) are shown in figure 3. After ablation 2313 rhythm strips were transmitted by all 41 patients and analyzed. The average heart rate in sinus rhythm per month was 65, 64 and 61 bpm at month 1, 2 and 3, respectively. When analyzed per week (as shown in figure 2), the average heart rate in the week after ablation was significantly higher than the week before ablation ($p<0.02$). The heart rate remained high, till it returned to pre-ablation values at week 12 (figure 2).In 249 rhythm strips (10.8%) of 20/41 patients (49%) AF was documented ($p< 0.002$). It occurred only once in 5, and twice in 3 patients, four times in the first month after ablation. Atrial flutter and atrial tachycardia were recorded respectively in 91 rhythm strips in 12 patients (4%, combined with AF in 6/41 patients). Only 2 of these 12 patients had only one event. The number of flutter and tachycardia events

was not lower in comparison to before the PVI, and the number of patients was not different either. One of the 3 arrhythmias was recorded in 24/41 patients ($p<0.01$).

The AF burden became 11.8% at 1, 10.1% at 2, and 11.9% at 3 months (figure 3). The reduction versus baseline was highly significant at all measurements. When all atrial arrhythmias were combined, the burden became 16.3% at 1, 14.4% at 2, and 17.9% at 3 months (figure 3), also highly significant each month. Only 63% of AF episodes before and 66% after ablation were symptomatic.

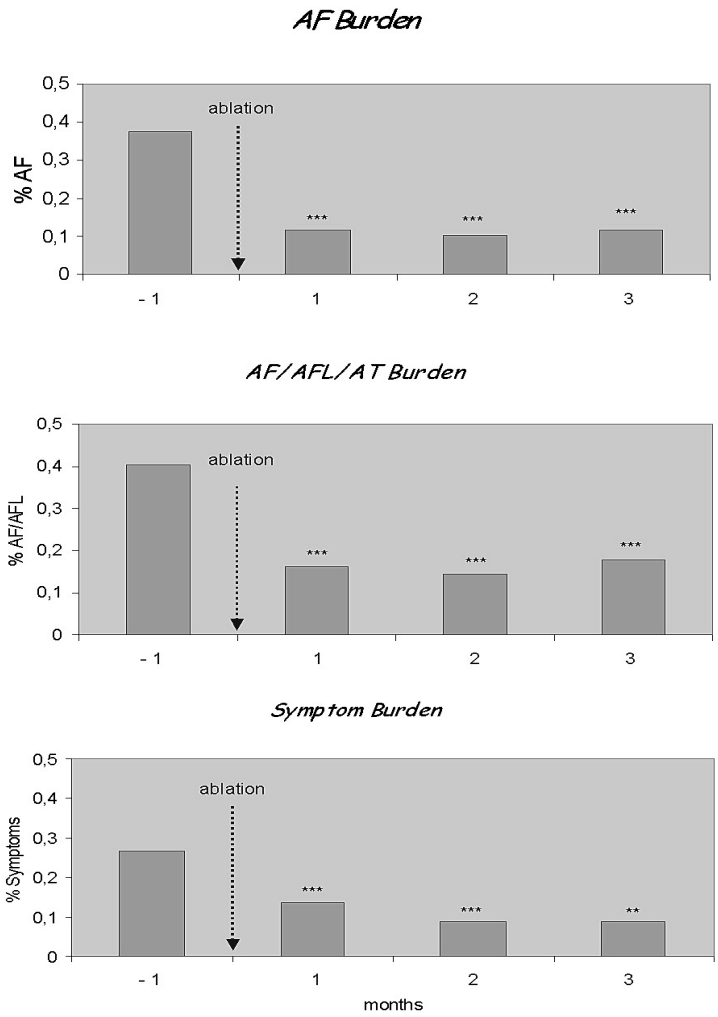

Figure 3: Graphic representation of the average monthly AF burden combined atrial arrhythmia burden and the symptom burden inthe month before and the 3 months after PVI.

Symptom burden

The symptom burden before and after ablation is presented in figure 3. Symptom burden significantly decreased over time (26.8 % before, and 13.8%, 8.9% and 8.7% at months 1, 2 and 3). Symptoms were absent in only 13% of patients before, and in 38, 47 and 62% of patients at these points in time during follow up (all $p<0.0001$ versus baseline). Atrial flutter contributed significantly to the symptom burden. More than 5 symptomatic days were recorded in 8/10 patients with atrial flutter after antral PVI. This occurred in only 8/20 patients with recurrences of AF alone ($p<0.058$).

Evaluation based on the combined results of Holter-ECG, event recordings and symptom score

The outcome of the symptom score matches the results of the Holter-ECG analysis. The vast majority of patients (83%) reported a clinical improvement.

Two patients experienced several highly symptomatic periods of atrial flutter, necessitating cavotricuspid isthmus ablation. This had a significant impact on the symptom score. Judged on the results of the event recordings, the success rate of antral PVI is less impressive. Only 49% of patients did not show any episode of AF after ablation. However, 8 of the other patients (19%) showed only one or two episodes of AF in the first month after ablation. Longer follow-up is needed to judge the impact of this finding.

Pulmonary vein diameter

No stenosis, defined as a reduction of diameter of more than 25%, was seen at the evaluation at 3 months.

DISCUSSION

The large variability in the reported success rates after PVI is not only dependent of the operator experience but also of the method of follow-up and the endpoints used(4). We report the initial results and follow-up after intracardiac echocardiography guided antral PVI in our institution.

We feel that only a comprehensive follow up as used in this study can provide us with usable data. Questionnaires are subjective, certainly when performed by the operator. Holter-ECG is a very objective measure, but gives only a snapshot of the entire observation period. Therefore, it can lead to an underestimation of the recurrence incidence. Event recording has its own limitations (including that it reveals a short snapshot), but it can be more tightly linked to symptoms.

Clinical success

Questionnaires as performed by an independent researcher may avoid the bias present in a physician-patient relation, and may reveal a true estimate of the clinically perceived success. This was very high, and reflects that PVI really improves quality of life in most patients. The outcome of the symptom score matched the results of the Holter-ECG. The symptom burden on the other hand, was impacted by highly symptomatic episodes of atrial flutter, as the patient experienced this often AF.

Holter-ECG`s

The Holter recording before the procedure gave a good impression of the highly symptomatic patient group which was studied. Most, but not all patients had AF, and the duration was impressive (roughly one third of the recording time). The conventional 24-hours Holter ECG gives only a snapshot of a desired observation period. Therefore, it can lead to an underestimation of the endpoints, and most researchers do now agree that this is a very weak investigational tool. However, it yields information which is complete over the recorded time period, with data on potential triggers (bradycardia, APC`s, atrial runs). It is clear from our data that a 24-hours recording leads to an underestimation of the real incidence of recurrence, and has a limited value. Therefore, researchers and clinicians have extended the Holter duration to 48 hours, and more recently to 7 days, which is also commercially wide spread (11), This method reveals indeed more asymptomatic recurrences than our 24-hour snapshot.

Transtelephonic event recording

Event recording provides us with a more reliable success rate of the procedure than 24-hour Holter recording. It does not cover the entire observation period, but is more strongly linked to symptoms. With this method, the intensity can further be increased to two or three recordings per day. We scheduled a daily transmission even when patients were asymptomatic, which was not always followed. Therefore, it is possible that the incidence of asymptomatic AF episodes is even higher than the reported rate. Senatore et al (12) were the first to show that asymptomatic periods of AF can be demonstrated by using transtelephonic electrocardiographic monitoring. The proportion of asymptomatic AF episodes (34-37%) before and after PVI in our series was comparable with other recent findings (11). The finding of asymptomatic AF has consequences for the continuation of anticoagulation and eventually antiarrhythmic drugs. Event recording also allows analysis of the time course of events (as we observed that some patients had few recurrences, with a tendency to occur early after the intervention), and to study potential triggers as bradycardia, and to

deal with other recurrent arrhythmias, which were often interpreted by the patient as being a recurrence.

Heart rate

An increase in average heart rate after PVI has been described, and was related to vagal denervation (13). We could confirm this observation, even when systematically bisoprolol was prescribed after PVI. Further, it was observed both with event recording and Holter-ECG, that heart rate returned to baseline values at 3 months. The explanation that autonomic influences are responsible for both changes is therefore acceptable.

Atrial flutter and tachycardia

Although not fully understood atrial flutter and AF often co-exist. In patients with both arrhythmias the atrial flutter often does not recur after successful antral PVI probably because pulmonary vein ectopy also triggers atrial flutter(14). As result of the formation of large unexcitable areas with ablation, the substrate for re-entrant arrhythmias (especially left atrial flutters) can be created(15). The incidence of left atrial flutter in a large series of antral PVI was reported to be 3.1% and related to recurrence of conduction from pulmonary vein to left atrium(16). Atrial flutter (typical and atypical) after PVAI is more common in patients with AF after previous cardiac surgery(17). In this series, atrial flutter or atrial tachycardia after antral PVI was detected in 12 patients, of which 6 had also AF recurrences. Two patients without AF recurrences underwent a successful right atrial isthmus ablation after the PVI. In the other patients symptoms were too infrequent to justify an electrophysiological mapping study, therefore no information about the critical isthmus in these patients is available. It was striking that more symptoms were reported by patients with both flutter and AF than by patients with AF alone.

Complications

Although PV isolation has become an accepted strategy in the treatment of AF, several complications were described. PV stenosis gained a lot of attention, but its incidence seems to decline with more proximal ablation(18). The use of intracardiac echocardiography allowed us to ablate in the antrum of the PVs and to prevent stenosis to occur. Thromboembolic complications of left atrial ablation procedures necessitate the intensive anticoagulation used in this study. Damage to the phrenic nerve is possible, especially in ablation at the ostium of the right superior PV. Unfortunately, and despite provocative pacing before ablation, this complication occurred once in this series. The most feared complication is esophageal perforation(19), necessitating power titration for instance with intracardiac echocardiography. These

serious, infrequent complications make a very high success rate necessary in order to make this procedure acceptable.

Study limitations

The follow-up period is too short to make firm conclusions. However, the high success rate and the absence of severe complications are promising. Three of the patients with recurrences underwent a second procedure. Two of these 3 patients are now without AF recurrences.

The reported fluoroscopy time is rather long and due to the learning curve involved in the technique of antral PVI. The intensity of the follow-up could be increased by using semi-permanent, automatic arrhythmia detecting, event recorders.

CONCLUSION

The clinical improvement after antral PVI is impressive. Daily transtelephonic monitoring allows a better assessment of the incidence of recurrences than Holter-ECG and symptom reporting. Intracardiac echocardiographically guided antral PVI significantly reduces symptomatic and asymptomatic AF episodes, but other arrhythmias interfere with the perceived clinical success. One third of AF episodes are asymptomatic.

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Chapter 16

SUMMARY

Atrial fibrillation (AF) is the most frequently encountered arrhythmia in clinical practice. Physicians of almost all specialities have to deal with this arrhythmia and its consequences. The incidence of AF rises proportional with age. 75 % of patients with AF are older than 75 years.

AF is not a benign disease. It can result in symptomatic palpitations, symptoms of pump failure, and above all an increase in the incidence of thrombo-embolic events like stroke. In the Framingham study it was shown that AF also independently increases mortality. In patients with heart failure the presence of AF further increases the risk of death.

For a long time the only therapy available to the treating physician was digoxin. Today the therapeutic options are too numerous to cover in one thesis, however, they options are mentioned briefly in chapter one.

Part 1 (chapters 2, 3 and 4) is dedicated to electrical cardioversion of AF. Electrical cardioversion was introduced in 1962 by Lown. We compared cardioversion with monophasic and biphasic waveforms and found no difference in efficacy. However less energy is needed for successful cardioversion using a biphasic waveform.

Our studies using a modified echocardiography probe for transesophageal cardioversion proved to be exciting. Transesophageal cardioversion was well tolerated by patients, the energy needed for cardioversion proved to be very low, and the intracardiac flow could be studied.

Part 2 of this thesis (chapters 5 and 6) is dedicated to the prevention of thromboembolic complications of AF. In chapter 5 we report the first Dutch experience using a catheter based left atrial appendix occluder. Chapter 6 is a review article covering current guidelines concerning anticoagulation in AF and atrial flutter patients.

Part 3 (chapter 7) and parts of the introduction are dedicated to the potential role of pacing in the treatment of AF. The role of pacing is obvious in patients with a sick sinus syndrome with bradycardia and those in whom AV node ablation is performed for rate control. In patients without an indication for pacemaker, however, the impact of special designed pacing algorithms on the recurrence rate of AF is disappointing. The Holter-ECG function of modern pacemakers is, however, of importance for research.

Part 4 (chapters 8-15) is dedicated to pulmonary vein isolation (PVI) as a strategy in AF treatment.

The pathophysiology of AF is the topic of chapter 8. Based on the multiple wavelet theory the (surgical) maze operation was developed. The success of the maze procedure stimulated research in catheter ablation. The first approach was to copy the maze procedure with linear ablation. We evaluated the use of intracardiac echocardiography during right sided linear ablation (chapter 9).

A major breakthrough in AF treatment was the development of pulmonary vein isolation. The goal of this approach is to isolate the triggers of AF located in the myocardial sleeves surrounding the pulmonary veins.

A much feared complication, especially in the early experience, was pulmonary vein stenosis. We showed (chapter 11 and 12) that multi-slice CT scanning is a useful tool to evaluate the diameter of the pulmonary veins in time.

Our first experience in PVI was with cryothermal ablation (chapter 10). Our success rate using this technique was moderate; pulmonary vein stenosis, however, was not seen.

Another way of preventing pulmonary vein stenosis is to ablate more proximally in the left atrium. PVI using intracardiac echocardiography (chapter 14) is a promising technique. Ablation at the os of the pulmonary veins is avoided and the delivery of ablation energy can be titrated.

PVI is much debated in the literature. Because patients with paroxysmal AF can have asymptomatic episodes, intensive follow-up is warranted. This is covered in chapter 15.

SAMENVATTING

Atriumfibrillatie (AF) is de meest voorkomende ritmestoornis in de klinische praktijk. Vrijwel elke arts komt met deze ritmestoornis of de gevolgen ervan in aanraking. De incidentie van AF neemt proportioneel toe met het stijgen van de leeftijd met als gevolg dat meer dan driekwart van de patiënten met AF ouder is dan 75 jaar (Feinberg WM Arch Intern Med 1995, 155, 469-473). AF is allerminst een onschuldige aandoening. De gevolgen van AF zijn naast klachten over palpitaties en snelle hartslag, een achteruitgang van de cardiale pompfunktie, vooral een toename van de kans op trombo-embolische complicaties zoals het herseninfarkt. De Framingham studie ((Benjamin EJ, Wolf PA Circulation1998;98;946-952) toonde aan dat AF onafhankelijk het risico op overlijden verhoogd. Bij patiënten met hartfalen verhoogt de aanwezigheid van AF het risico op overlijden aanzienlijk (oa SOLVD (Dries DL, JACC 1998,32:695-703). Lange tijd had de behandeld arts slechts digoxine (vingerhoedskruid) tot zijn of haar beschikking. Het scala aan behandelingsmethoden is inmiddels zo groot, dat een complete behandeling ervan in een proefschrift onmogelijk is. In hoofdstuk 1 van dit proefschrift wordt hierop in grote lijnen wel ingegaan.

Deel 1 (de hoofdstukken 2, 3 en 4) is gewijd aan de cardioversie van AF. Het elektrisch cardioverteren van AF naar sinusritme werd in 1962 door Lown (Lown B. JAMA 1962;182:548-555) geïntroduceerd. Het verschil tussen cardioversie met monophasische en biphasische shocks was onderwerp van studie. We vonden geen verschil tussen beide vormen in effectiviteit zij het dat voor biphasische cardioversie minder energie nodig was. Bijzonder boeiend was het onderzoek met een gemodificeerde transoesophagale echocardiografie probe, geschikt gemaakt voor cardioversie. De transoesophagale cardioversie werd door patiënten goed verdragen, de benodigde energie bleek zeer laag en de effecten van cardioversie op de hemodynamiek van de boezems goed te onderzoeken.

Deel 2 van dit proefschrift (hoofdstuk 5 en 6)is gewijd aan de preventie van tromboembolische complicaties. Als eerste in Nederland deden we ervaring op met het afsluiten van het hartoortje van de linker boezem middels een via een catheter ingebracht uitvouwbaar apparaatje. In een uitgebreid overzichtsartikel vatten we de huidige richtlijnen en inzichten omtrent orale antistolling bij AF patiënten samen.

Deel 3 (hoofdstuk 7)en een deel van de introduktie is gewijd aan de rol van hartstimulatie (pacemakers) in de behandeling van AF. Deze rol is duidelijk bij patiënten waarbij gekozen is voor acceptatie van het AF en regulatie van de hartfrequentie middels Hisbundel ablatie en implantatie van een pacemaker. Ook bij patiënten die

een traag hartritme afwisselen met atriumfibrilleren (het brady-tachy syndroom of het sick sinus syndrome) is deze rol duidelijk. Bij andere patiënten is de rol van pacemakers teleurstellend. De holter funktie van pacemakers is evenwel belangrijk voor wetenschappelijk onderzoek.

Deel 4 van dit proefschrift (hoofdstuk 8 tot en met 15) is gewijd aan de rol van catheter ablatie voor de behandeling van AF. In hoofdstuk 8 wordt ingegaan op de pathofysiologie van AF. Op grond van de theorie dat AF slechts kan bestaan als er in de boezems van het hart tegelijkertijd meerdere cirkelstroompjes (wavelets) bestaan werd de maze operatie ontwikkeld. Het succes van de maze operatie was een stimulans voor ontwikkeling van catheterablatie als behandeling van AF. Allereerst werd de mogelijkheid van lineaire ablatie onderzocht. Wij deden ervaring op met de toepassing van intracardiale echocardiografie tijdens lineaire ablatie in de rechter boezem. Een revolutionaire ontwikkeling was die van de pulmonaal vene isolatie. Doel is de prikkelvorming in de mouwtje van spierweefsel in deze venen, die AF kunnen veroorzaken, te isoleren. Het optreden van pulmonaal vene stenose is een gevreesde complicatie van de oorspronkelijke ablatietechniek. We toonden aan dat multi-slice CT scanning een goede methode is om de diameter van de pulmonaalvenen in de loop van de tijd te vervolgen. Onze eerste ervaringen met pulmonaal vene isolatie was met cryo-energie. Het succespercentage met cryothermale pulmonaal vene isolatie was beperkt, maar pulmonaalvene stenose werd niet gezien (hoofdstuk 10). De kans op deze complicatie is aanzienlijk verkleind indien meer proximaal in de linker boezem wordt geableerd. Catheter ablatie onder geleide van intracardiale echocardiografie is een veelbelovende techniek waarbij ablatie in de oorsprong van de pulmonaal vene (os) wordt voorkomen en de hoeveelheid energie goed getitreerd kan worden (hoofstuk 14). Over pulmonaal vene isolatie verschenen inmiddels zeer veel publicaties. Omdat patiënten met AF ook symptoomloze perioden kennen is het noodzakelijk om na een ablatiebehandeling te zorgen voor een intensieve follow-up. Dit aspect wordt behandeld in de hoofdstuk 15.

DANKWOORD

Gaarne wil ik op deze plaats allen bedanken die op enigerlei wijze hebben bijgedragen aan de totstandkoming van dit proefschrift.

Als eerst wil ik mijn promotor Prof. dr. L. Jordaens bedanken voor zijn bijdrage aan dit proefschrift. Beste Luc, zonder jou was dit proefschrift niet tot stand gekomen. Jij hebt mij de kans gegeven me te specialiseren in de elektrofysiologie en daar ben ik je zeer dankbaar voor. Ik hoop van ganser harte dat je de afdeling verder kunt ontwikkelen en dat we contact houden.

Graag wil ik de overige leden van mijn promotiecommissie, Professor Jos Roelandt, Professor Peter Koudstaal en Dr Isabelle van Gelder, van harte bedanken voor het beoordelen van mijn proefschrift.

Het verdedigen van mijn proefschrift markeert het einde van mijn periode in het Erasmus MC. In de 5 jaar die ik gewerkt heb in het thoraxcentrum heb ik buitengewoon goed samengewerkt met alle collega's van de afdeling Cardiologie.
In Prof.dr. Maarten Simoons, dank ik u allen hartelijk.

Een speciaal woord van dank wil ik richten aan alle leden van het team van de afdeling Klinische Elektrofysiologie: Richard Alloway, Frans Beurmanjer, Laura Bom, Lara Emilsdottir, Wilma van der Kerke, Paul Knops, Ronald Luyten, Agnes Muskens, Ronald van der Perk, Roel de Ruiter, Hans van Schendel, Detti Schilderman, Anneke Stam, Ton Verblauw en Esther Zwanenburg. Jullie inzet is fantastisch.

Ook speciale dank aan mijn collega's Marco Alings, Geert-Jan Kimman, Joris Mekel, Jan Res, Maximo Rivero-Ayerza, Tamas Szili-Torok, Dominic Theuns en Andrew Thornton. Het was een voorrecht met jullie te mogen werken.

Heel veel dank aan Petter Janse, je was onmisbaar in de data collectie en verwerking. Annet Louw was een uitermate belangrijke steun bij al het regelwerk dat nu eenmaal bij een promotie hoort.

Het werken met Jan Tuin aan illustraties en posters, met de muziek van Miles Davis op de achtergrond, vormde onvergetelijke momenten tijdens mijn Erasmus periode.

Veel dank ook aan de medewerkers van het ECG en Holter lab onder leiding van Angela Peterse-Dekkers.

Werken in het Erasmus MC is mede zo bijzonder door de contacten met buitenlandse collega's. Veel dank ben ik verschuldigd aan prof Itzhak Kronzon voor het beschikbaar stellen van zijn gemodificeerde transoesophagale echoprobe, aan Nassire Marrouche, MD voor de samenwerking op het gebied van de pulmonaal vene isolatie en aan Ruzcika Maksimovic voor haar werk met de multislice CT scan.

Mijn huidige collega's in het Medisch Spectrum Twente in Enschede dank ik hartelijk voor het in mij gestelde vertrouwen. De samenwerking met de afdeling elektrofysiologie van de Isala Klinieken in Zwolle is zeer hartelijk. Ik dank mijn collega's Willem Beukema, Arif Elvan en Arnand Ramdat-Missier hiervoor en hoop op een vruchtbare wetenschappelijke samenwerking

Ik ben vereerd dat mijn vrienden Drs. Bas Spelberg en Dr Mattijs Numans, met wie ik zoveel jaren geleden in Utrecht aan de studie geneeskunde begon, bereid zijn mij als paranimfen tijdens de promotie bij te staan.

Mijn ouders wil ik danken voor hun onvoorwaardelijke steun. Ik ben opgegroeid in een gezin waarin warmte gecombineerd was met stimuleren van een kritische houding en wetenschappelijke belangstelling.

Ten slotte, en eigenlijk had ik hier mee moeten beginnen, ben ik de grootste dank verschuldigd aan Truus. Zonder jouw liefde, steun en altijd wijze advies, was dit proefschrift niet van de grond gekomen.

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CURRICULUM VITAE

The author of this thesis was born on March 28, 1958, in Sittard, the Netherlands. He graduated in 1976 at the Albert Schweitzer Scholengemeenschap in Geleen: Atheneum-B certificate.

From 1976 to 1984 he studied medicine at the University of Utrecht. After graduation he worked as a house-officer at the department of Internal Medicine at the Zeister Ziekenhuis in Zeist. As a part of the training in Cardiology he studied Internal Medicine from September 1985 to September 1987 at the Diaconessenhuis in Arnhem (chairman Dr. C. van Gastel). In September 1987 the speciality training Cardiology started at the department of Cardiology of the ziekenhuis Leyenburg in The Hague (chairman: Dr C. Sparling) followed by training at the Academisch Ziekenhuis in Leiden (chairman: Prof. Dr. A. Bruschke). He was registered as a cardiologist in September 1990.

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