Evaluation of New Non-Pharmacological Therapies for Symptomatic Atrial Fibrillation

*With Special Emphasis on the Maze Procedure*

BY

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ABSTRACT

atrial fibrillation: with special emphasis on the Maze procedure. Acta Universitatis
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Atrial fibrillation is a common disease. With pharmacological therapy most patients
with atrial fibrillation have moderate or light symptoms, but a number of patients have
severely symptomatic disease. This study evaluates two new non-pharmacological
therapies for atrial fibrillation, the Maze procedure and atrial overdrive pacing.

In the patients planned for Maze surgery, the quality of life, assessed with the SF-36
questionnaire, was very low before the operation. The quality of life was markedly
improved 6 and 12 months after the Maze operation, and was comparable to values of
the general Swedish population.

In the patients with sinus rhythm before surgery, the atrial size and transport function
was assessed with echocardiography, and the autonomic balance was assessed with heart
rate variability (HRV). The sizes of both atria were reduced and the transmitral
early/atrial filling velocity (E/A) ratio was increased at 6 months after the operation
compared to before. A gradual increase of the E/A ratio was seen during the 24 months
follow-up period, indicating a progressive decline of the left atrial transport function.

All components of HRV, including the parameters expressing sympathetic and
parasympathetic modulation, had markedly decreased early after the Maze procedure
compared to before. Late after the operation all components of HRV were still markedly
depressed. This is interpreted as a partial autonomic denervation of the heart.

Single-site right atrial overdrive pacing with two different levels of overdriving was
compared with no pacing in patients with paroxysmal atrial fibrillation in a cross-over
study. Overdrive pacing reduced the median number of episodes of atrial fibrillation with
50% compared to no pacing. There was no difference in efficacy between medium rate
overdrive pacing and high rate overdrive pacing.

Key words: Atrial fibrillation, Maze procedure, pacing, quality of life.

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List of original papers

The present thesis is based on the following original papers, which will be referred to by their Roman numerals.


IV. Effects of right atrial overdrive pacing for the prevention of symptomatic paroxysmal atrial fibrillation - a multicenter randomized study - the PAF-PACE study. S Wiberg, S Lönnernlom, S Jensen, P Blomström, I Ringqvist, C Blomström-Lundqvist. Submitted

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Abbreviations

AF     atrial fibrillation
ANS    autonomic nerve system
AV     atrio-ventricular
A wave atrial filling wave
bpm    beats per minute
CABG   coronary artery bypass grafting
ECG    electrocardiogram
E wave early filling wave
HF     high frequency
HRV    heart rate variability
LF     low frequency
LV-EF  left ventricular ejection fraction
PAF    paroxysmal atrial fibrillation
SD     standard deviation
SDNN   standard deviation of normal to normal beats
**Background**

**History**
There is an ancient description of irregular pulse in The Yellow Emperor’s Classic of Internal Medicine by Huang Ti Nei Ching Su Wen written between 1696-1598 BC, which might be the first description of atrial fibrillation (1). In recorded history, William Harvey was probably the first to describe "fibrillation of the auricles" in animals in 1628. Harvey was convinced that systole, rather than diastole, was the active part of the cardiac cycle, which starts in the atria. However, it was not until a graphic method for investigation of the pulse was invented in the mid-nineteenth century that Nothnagel was able to publish three arterial pulse curves typical of the irregular heartbeat in 1876. He called the irregular arrhythmia with continuous changes in the height and tension of the pulse waves, delirium cordis. In 1907 Cushny and Edmunds established in experiments that the irregular pulse known as delirium cordis was caused by auricular delirium (2).

The main diagnostic breakthrough for AF was the invention of the electrocardiograph by Einthoven in 1900 (1). In 1909 Lewis and Rothberger and Wintherberg independently compared ECG recordings from animals with experimentally induced atrial fibrillation with those from patients with arrhythmia perpetua and noted three points of resemblance: absolute ventricular arrhythmia, the absence of P waves, and the presence of irregular oscillations of the venous galvanometer string caused by the fibrillatory waves themselves (2).

In 1914 Garrey presented the first modern theories regarding the mechanisms of atrial fibrillation (3). His experiments showed that impulse blocks were transitory and shifting in nature but that they forced the contraction wave into other, more circuitous paths, facilitating a series of ring-like circuits of shifting location. In 1962 Moe proposed that atrial fibrillation is a self-sustaining arrhythmia independent of focal discharge, which depends on random fractionation of the wavefronts as they propagate around islands of refractory tissue - the multiple wavelet hypothesis. The number of wavelets present at any time depends on the refractory period and delayed conduction velocity in different parts of the atria (4). This hypothesis was later experimentally supported by Allessie and co-workers in 1977 (5,6). Allessie’s group also demonstrated in an animal model, that AF begets AF, meaning that AF induces electrophysiological and later structural changes in the atrial myocardium that help to maintain AF (7).
Definition

Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of the atrial mechanical function. On the ECG, AF is described by the replacement of consistent P waves by rapid oscillations or fibrillatory waves, which vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response when AV conduction is intact (8).

Classification

Various classification systems have been proposed for AF (9,10). Most systems use the temporal pattern of AF as a basis for classification. If the duration of an AF episode is less than 48 hours, AF is designated acute; when the duration of AF is above 48 hours, AF is designated chronic (11).

In the recently presented guidelines for management of patients with atrial fibrillation by ACC/AHA/ESC (12), a classification system is recommended that distinguishes between a first-detected episode of AF and recurrent AF. If AF is recurrent, it is designated paroxysmal if the arrhythmia terminates spontaneously; when AF is sustained, it is designated persistent. The latter designation is not affected by pharmacological or electrical cardioversion. If AF is sustained, and cardioversion has failed or not been attempted, AF is designated permanent. The term lone AF has been variously defined but generally applies to AF in the absence of evidence of structural heart disease (11).

Epidemiology

Atrial fibrillation is the most common arrhythmia encountered in clinical practice with an overall prevalence estimated at 0.4% of the general population (13). The prevalence increases with advancing age, being below 1% in those under 60 years and almost 9% in those above 80 years (14). AF is more common in men than in women (15). It has been estimated that a total of 93000 individuals suffer from permanent AF in Sweden (16). The incidence of AF increases gradually from less than 0.1% per year in those below 50 years of age to about 2% in those above the age of 80 years (15). There are studies indicating an increasing incidence of AF over the last 30 years (17).

Episodes of AF can be secondary to several factors including thyrotoxicosis, surgery, respiratory infections, pulmonary embolism, myocardial infarction, pericarditis, other supraventricular arrhythmias or alcohol intake. The most common disorders associated with AF are, however, cardiovascular diseases. The cardiovascular diseases most often associated with AF are hypertension, ischemic heart disease and congestive heart failure. Mitral stenosis, previously a disease frequently associated with AF, rarely causes AF these days (18). In about
30% of the cases with persistent or paroxysmal AF, there is no associated disease whatsoever (15,19).

Pathophysiology

Initiation and perpetuation of AF

Premature atrial contractions preceding the onset of AF have been suggested as the initiating factor for AF (20). However, premature atrial contractions are frequent and in most instances they do not initiate AF (21). Besides a triggering factor, such as premature atrial contraction, certain electrophysiological properties of the atrial myocardium are necessary to initiate AF. Reentry arrhythmias, including AF, are initiated by a wave front hitting an area of local, unidirectional conduction block, and a conduction time that is long enough to permit the impulse to travel around the block and excite depolarized fibers proximal to the block (22). The susceptibility to reentry arrhythmias is thus dependent on the atrial refractory period and conduction velocity, i.e. the wavelength. Allessi and colleagues have previously shown that the inducibility of reentrant arrhythmias and the size of functionally determined intra-atrial circuits depend on the wavelength of the atrial impulses (23). In one study, AF was exclusively induced in normal hearts under conditions in which the wavelength was short (23). ANS, described in more detail in the next section, can affect the wavelength, but the role of the ANS in the initiation and perpetuation of AF is yet unclear.

Some authors suggest that particular areas of the atrial myocardium are involved in the initiation of AF (24). The sites of inter-atrial conduction and the electrophysiological properties of these connections have been studied recently (25). The conduction over the posterior inter-atrial connection has been found to be slow in patients with paroxysmal AF (25), but the role of this finding in the initiation and perpetuation of AF is still unknown. Heterogeneity of structural and electrophysiological properties, as seen in patients with organic heart disease, is thought to play an important role in the initiation and perpetuation of AF, since it increases the likelihood of unidirectional block after premature impulses (26,27).

The multiple wavelet hypothesis (4), proposed by Moe and colleagues and later confirmed in an animal model by Allessi and coworkers (5,6), has gained widespread acceptance. This hypothesis postulated that perpetuation of AF was based on wave fronts that randomly fractionate around islands of refractory tissue into daughter wavelets of various size. Some of these daughter wavelets meet other wavelets or boundaries and die, while others propagate through excitable tissue, encountering areas of refractory tissue, fractionating around
these areas, giving rise to new wavelets in the continuous motion characterizing AF.
The size of the atrial mass is in theory also an important factor in the initiation and maintenance of AF, since a large myocardial mass can harbor a sufficient number of wavelets to maintain AF despite longer wavelengths. Large left atrial size has long been associated with AF, but it has been debated whether this was the cause or consequence of AF (28). However, a large, prospective study has recently established that an enlarged left atrial size was a strong predictor of patients developing AF in the study (29).

Another theory concerning the mechanisms of AF involves enhanced automaticity in one or several rapidly firing foci. The depolarizations are so rapid that areas of tissue are still refractory, and the wave front is fractionated into multiple wavelets, as in multiple-wavelet reentry. This theory is supported by experimental studies of aconitin-induced AF in which a rapidly depolarizing focus initiated AF (30). This theory has been supported by recent human studies in which spontaneous rapidly firing foci in the pulmonary veins initiated episodes of AF (9). Similar rapidly firing foci have also been observed outside the pulmonary veins, in the right atrium, and in the superior vena cava, although less frequently (31). The relevance of these foci to clinical episodes of AF has been confirmed by the fact that AF was cured after catheter ablation of the observed focus (9,31-33). Whether this represents a particular form of AF or a triggering arrhythmia is not clear.

Remodeling
It is a clinically well-known fact that the success rate of converting atrial fibrillation, either pharmacologically or electrically, is higher in AF of recent onset than in long-standing AF (34-35). This phenomenon could be due to the progression of a pathological process in the myocardium, responsible for the initiation of AF, or a secondary process caused by AF itself. Wijffel’s study showed that induced AF gradually became more and more sustained and less likely to terminate spontaneously the longer AF was maintained by pacing (7). The gradual change in the propensity for AF was accompanied by a gradual shortening of the effective atrial refractory period, a phenomenon known as electrical remodeling. The electrical remodeling was observed within 24 hours of AF. Similar electrical remodeling has later been confirmed in the human atrium (36-38). The mechanisms responsible for this electrical remodeling are not completely understood, but reduced levels of L-type calcium currents and changes in several potassium channels have been observed in patients with AF (36-37).
A mechanical remodeling is noted later on in the time-course of persistent AF, with reduced contractile force (39). In animal models the electrical remodeling was completely reversed after 7-14 days of sinus rhythm, but the cellular and morphological remodeling was not reversed (39). This is in concordance with the high risk of recurrence of AF soon after cardioversion (40). Following cardioversion of long-standing AF in humans, blunted atrial contraction has been observed soon after cardioversion, with a gradual recovery over several weeks (41). The structural and electrophysiological changes responsible for the conversion of paroxysmal or persistent AF to permanent AF are so far unknown.

*Autonomic nervous system*

The role of the autonomic nervous system in the initiation and perpetuation of AF is not completely understood. Experimentally, it has been observed that both parasympathetic and sympathetic stimulation can be profibrillatory (42-43). Some authors have proposed that a subgroup of patients have AF of primarily vagal or adrenergic origin (9). Vagally induced AF is described to occur in middle-aged patients in the absence of any structural heart disease (9). The mechanisms by which the autonomic nervous system facilitates AF in humans is, however, not completely understood.

Some of the main functions of the ANS are to regulate blood pressure, heart rate, and the oxygen and glucose supply to the different tissues of the body. Afferent (to the central nervous system) input comes from pain receptors, baroreceptors, stretch receptors in the atria and the lungs, and different chemoreceptors (44). The ANS acts mainly through reflexes, of which some are initiated in the spinal cord and others in higher brain centres, including the hypothalamus. The efferent limb of ANS consists of two divisions, the sympathetic and the parasympathetic division, which are anatomically and functionally distinct. Both parasympathetic and sympathetic fibers innervate the heart, and under most circumstances there is tonic activity in both limbs of ANS (45).

The parasympathetic fibers originate in the brain stem and subsequently form the right and left vagal nerves. Cardiac branches of both the right and left vagal nerves innervate the intracardiac parasympathetic ganglia located in the subepicardial tissue (46). The vagal pathways to the sinus node pass through a fat pad between the superior caval vein and the root of the aorta, transmitting to postganglionic neurons located in a fat pad adjacent to the right pulmonary vein-atrial junction (47). Stimulation of the parasympathetic nerves results in slowing of the heart rate, prolonged AV-node conduction, and shortening of the atrial refractory period (47,48). The effect of vagal stimulation on the conduction velocity in humans has not been established, but in dogs vagal stimulation did not result in any changes in the conduction velocity (49).
Recently, it was shown experimentally that parasympathetic denervation, with subsequent vagal supersensitivity, could produce shortening of the atrial refractory period (47). The authors speculated that focal denervation in the atrial myocardium and subsequently denervation supersensitivity might play a role in the genesis of atrial arrhythmias (47).

The preganglionic sympathetic fibers originate in the cervical and thoracic part of the spinal cord. The preganglionic fibers innervate the postganglionic fibers in the stellate ganglia and the paravertebral ganglion chain (50). The postganglionic sympathetic nerve fibers innervate the heart through a number of cardiopulmonary nerves, of which many run along the coronary arteries. The sympathetic nerves form the cardiac plexus together with the parasympathetic nerves dorsal to the pulmonary artery (51). The anatomy of the sympathetic innervation to the sinus node has to my knowledge not been elucidated in humans.

Stimulation of the sympathetic nervous system results in a shortening of the atrial refractory period both during sinus rhythm and during AF (52-55). No significant change in the atrial conduction velocity has been found following adrenergic stimulation (49). Several studies have addressed the issue of autonomic balance preceding the onset of AF by HRV measurements, but with conflicting results (56-58). The role of the autonomic nervous system in the initiation and perpetuation of AF in humans is thus still unclear.

The heart rate is normally determined by the rate of depolarization of the cardiac pacemaker tissue, normally the sinus node. The intrinsic depolarization rate of the sinus node, in the absence of any neurohumoral influence is about 100 bpm (59). The ANS regulates the heart rate according to the demand for cardiac output of blood, with stimulation of the parasympathetic nerves slowing the rate and stimulation of sympathetic nerves accelerating it (60). In most circumstances, both limbs of ANS are under tonic activation with the vagal effects dominating (45). The latency of a response of the sinus node to vagal stimulation is very short with the peak response in the first or second beat after stimulation. This is in contrast to the response to sympathetic stimulation, which has a latency period of up to 5 seconds, followed by a gradual increase in heart rate (44).

Consequences of AF
Atrial fibrillation can be symptomatic or asymptomatic. Symptomatic patients with AF complain of palpitations, dyspnoea, fatigue, lightheadedness, syncope, or chest pain. Most patients have moderately severe symptoms, but a number of patients have severe symptoms that greatly affect their quality of life (61). The severity of symptoms is not well correlated to concomitant cardiovascular
disorders (62) and many patients with lone, paroxysmal AF have an impaired quality of life (63).

Atrial fibrillation results in the loss of atrial mechanical function, an irregular ventricular response, and often an inappropriately rapid ventricular rate, leading to hemodynamic impairment. During AF cardiac output may be reduced by up to 25% (64). A marked reduction in cardiac output may occur in patients with impaired diastolic ventricular function, such as in those with hypertension, hypertrophic cardiomyopathy, or mitral stenosis (65). Moreover, a persistently elevated ventricular rate can produce a type of dilated cardiomyopathy named tachycardia-induced cardiomyopathy. This cardiomyopathy is especially important to recognize since it can be reversed by ventricular rate control (66,67).

The most frequent complication of AF is, however, stroke. Large epidemiological studies have found that the risk of ischemic stroke among patients with non-valvular AF is approximately 5% per year, representing a 5 to 7-fold increase as compared to patients without AF (14,68,69). In addition to these clinical strokes, silent infarcts detected by computer tomography have been found in 35-37% of patients with non-rheumatic AF (70,71). The embolic risk increases with age and the presence of coexisting cardiovascular diseases such as hypertension, congestive heart failure, rheumatic valvular disease, diabetes mellitus and a history of previous stroke. The risk of embolic stroke in patients age 60 years or younger with lone AF is very low (72).

Management of atrial fibrillation
The management of AF depends on the nature of the disease. In patients with paroxysmal AF, the goal is to prevent recurrences of AF episodes. In patients with persistent AF, there are two different ways of managing the arrhythmia: to restore and maintain sinus rhythm or to allow AF to become permanent and ensure that the ventricular rate is controlled. Cardioversion to sinus rhythm offers the benefit of alleviating symptoms, improving hemodynamics (73) and exercise capacity (73) and possibly reducing the risk of thromboembolism. However, the recurrence rate is high, and the antiarrhythmic drugs used to prevent recurrences have frequent side effects. Despite the high incidence of AF, there are hardly any data supporting any of the strategies. In all patients, regardless of the type of AF and the decided strategy, prevention of thromboembolism must be considered.

Cardioversion
Cardioversion to sinus rhythm can be achieved by means of pharmacological or electrical conversion. Regardless of the technique of cardioversion, adequate
anticoagulation preceding the cardioversion is recommended if the duration of AF is more than 48 hours (12). The success rate of electrical cardioversion, introduced by Lown in 1962 (74,75), has been reported to be 70-94% (34,75,76). Pharmacological cardioversion has not been compared directly with electrical cardioversion, but it appears to be less efficacious (12). The different pharmacological agents have not been compared with each other in a controlled fashion, and there seem to be no clear superiority of one agent over the others. The pharmacological agents with proven efficacy are: dofetilide (77-79), flecainide (80-82), ibutilide (83,84), propafenone (85-87), amiodarone (88,89), and quinidine (34,90).

**Maintenance of sinus rhythm**
In the absence of any prophylactic pharmacological therapy, the recurrence rate after an electrical cardioversion is 60-80% within 12 months (35,76). Most of the relapses occur within the first few weeks after the cardioversion (40). Pharmacological therapy reduces the recurrence rate at 12 months after cardioversion to approximately 50% (91,93,97). Prophylactic effect against recurrences of AF has been observed for a number of pharmacological agents: amiodarone (91), disopyramide (92,93), dofetilide (79), flecainide (94), propafenone (73,95), quinidine (96,97) and sotalol (97,98). None of the drugs has convincingly proved to be superior to the others. Negative inotropic effects limit treatment with antiarrhythmic drugs for patients with heart failure, as does the risk of proarrhythmia (99). Prophylactic treatment is indicated in patients with troublesome symptoms related to paroxysmal AF or recurrence after cardioversion, since it is not yet known whether maintenance of sinus rhythm prevents thromboembolism, heart failure or death (12).

**Rate control**
In patients with permanent AF, or in those patients with persistent AF in whom a stable sinus rhythm cannot be achieved, the heart rate should be controlled. There are, however, different opinions about what is meant by controlled rate (100,101). In the recently published guidelines for the management of patients with AF, the rate is considered to be controlled when the ventricular response ranges between 60 and 80 beats/minute at rest and between 90 and 115 beats/minute during moderate exercise (12). The pharmacological agents that can be used to control the ventricular rate during AF are digitalis, beta-blockers, diltiazem, and verapamil. The predominant effect of digitalis is mediated through the autonomic nervous system by enhancing vagal tone on the AV node (102), which explains why digitalis does not slow the heart rate during exercise in patients with AF (103). Beta-blocking agents and the calcium antagonists
verapamil and diltiazem reduce the heart rate both at rest and during exercise (104). Often, a combination of drugs is necessary to control the ventricular rate.

Anticoagulation
There is a clear association between rheumatic valvular disease, atrial fibrillation, and stroke, thereby warranting the use of anticoagulation (105). The risk factors for stroke and the efficacy of antithrombotic therapy in non-rheumatic AF have been studied in a number of large, randomized trials (106-110), later combined into a meta-analysis (111). Warfarin decreased the frequency of all strokes by 68% compared to placebo, with an absolute annual reduction of 3.1%. Aspirin has been shown to decrease the risk of stroke by 19-36% (111,112). Recommendations about anticoagulation for the prevention of stroke in patients with AF were recently presented (12).

Non-pharmacological therapies
The limited efficacy of antiarrhythmic drugs has stimulated research to find non-pharmacological therapies that reduce the symptoms of AF and ultimately a curative therapy for AF.

Catheter ablation
In 1982, Scheinman and associates (113) introduced a technique for transvenous ablation of the His bundle. His bundle ablation produces a complete AV block, which allows the atria to fibrillate without affecting the ventricular rhythm. A rate-adaptive pacemaker is implanted before or during the procedure to stimulate the ventricles. His bundle ablation decreases subjective symptoms of AF and improves the quality of life of patients (114). His bundle ablation has therefore become a widely accepted non-pharmacological therapy for both symptomatic paroxysmal AF in patients where pharmacological therapy has failed and in patients with permanent AF where rate control is inadequate with pharmacological treatment (115,116). However, since both atria are allowed to continue to fibrillate, normal hemodynamics are not restored and the patients are still vulnerable to thromboembolic complications.

The high success rate of the surgical Maze procedure stimulated research with transcutaneous catheter ablation with ablation lines resembling the Maze procedure. Although feasible, these procedures were very complicated, with long procedure times, and only a minority of the patients were arrhythmia-free after the procedure (118-120).
The observation that a rapidly firing focal activity, most often located in the pulmonary veins, was the initiating mechanism of AF in a subset of patients with paroxysmal AF has resulted in attempts to treat AF by focal catheter ablation. Two different approaches to catheter ablation of the triggering foci have been reported in the treatment of patients with AF. Haissaguerre and co-workers initially performed distal ablations at the site of earliest spike activity (9). That technique was feasible but time-consuming and required frequent ectopic beats. Currently, the technique mostly used is distal ablation close to the pulmonary vein ostium of all pulmonary veins with the aim to electrically isolate the pulmonary vein activity. This is achieved by ablating inside the pulmonary veins at the sites where electrical potentials are recorded. The reported success rate has been close to 70%, although more than 50% of the patients needed a second ablation procedure (121,122). However, another center recently reported a success rate of only 33%, and 8.3% of the patients developed pulmonary vein stenosis (123). The other catheter-based approach, introduced by Pappone, aims at creating complete ablation lines around the ostia of the four different pulmonary veins. To avoid the complication of pulmonary vein stenosis, the radiofrequency lesions are applied > 5 mm from the ostia. Despite the fact that complete conduction block was seldom achieved, the technique has been successful in eliminating AF. A recently published paper (124) reports that 251 patients with AF (179 paroxysmal and 79 permanent) were treated with circular ablation around the pulmonary veins. After a mean follow-up of 10.4 months, freedom from AF was 85% for paroxysmal AF and 68% for permanent AF. The acute complication rate was reported to be 0.8%.

These two ablation procedures look very promising, but the long-term effects are yet unknown.

Open heart surgery
In 1980, Cox and co-workers (125) reported the development of a surgical technique, named “left atrial isolation procedure”, that was capable of isolating the body of the left atrium from the remainder of the heart. Experiments showed that atrial fibrillation could be confined to the left atrium while sinus rhythm persisted in the right atrium and the chambers (125). The procedure regulates the heart rhythm and diminishes symptoms of atrial fibrillation, but the increased risk of thromboembolic complications remains.

The corridor procedure, introduced in 1985 by Guirandon and colleagues (126), is a surgical procedure to treat atrial fibrillation by creating an electrically isolated corridor in the atrial myocardium between the sinus node and the AV node. In this way the sinus node is allowed to drive the ventricles and a regular ventricular rhythm is reestablished. However, because the remaining parts of the right and left atria are allowed to fibrillate, the normal hemodynamics of the
heart are not restored and the vulnerability to thromboembolic complications is the same as preoperatively.

The Maze procedure
Based on his previous experiences, Cox and co-workers (127) continued to work on a surgical treatment for AF that would result in ablation of AF, restoration of AV synchrony, and normal cardiac hemodynamics while reducing the patient’s vulnerability to thromboembolism. By means of computerized intraoperative mapping systems, it was observed that the multiple reentrant waves recorded during AF were so disorganized and unstable that time map-guided incisions would have no effect on the arrhythmia. The Maze procedure was created based on the principle that the only way to prevent the atrium from fibrillating was to interrupt all potential pathways for atrial macroreentrant circuits that have been identified (128).

Figure 1. The Maze III procedure (Annals of Thoracic Surgery 1993, reprinted with permission).
The Maze procedure is carried out during cardioplegic arrest during which both the right and left atrial appendages are excised and a number of incisions are made in the left and right atria, including a circular line around the pulmonary veins. The incision lines are then closed with sutures. The surgical incisions are combined with cryolesions closest to the tricuspid and mitral valves. The initial Maze procedure has gradually been modified into the Maze III procedure (Figure 1) because of the chronotropic incompetency that occurred in a high proportion of patients postoperatively (129).

Since the introduction of the Maze procedure in 1987 the method has been used by a limited number of centers. The procedure has been carried out mainly in combination with mitral valve surgery but also on its own. Patient characteristics and the surgical results of the Maze procedure reported in the literature are summarized in Table 1 (130-142).

Freedom from AF has been reported in 75-100% of patients after the procedure, with the lower figures reported by centers where the Maze procedure had been performed concomitantly with valve surgery in patients with permanent AF. The mortality risk associated with the procedure is low (0-4.9%) considering the fact that the majority of the patients included in the published studies have rheumatic valve disease or congenital heart disorders. The focus of the patients with concomitant cardiac diseases has been to improve hemodynamics by alleviating AF. In 20% of the patients described in the studies, however, the primary indication for surgery was symptomatic AF. In patients with severely symptomatic AF, the goal of the procedure is to alleviate symptoms of AF and improve quality of life without causing other morbidity. There are no data, however, on the effects on the patients’ quality of life, and very limited data regarding the effects on the mechanical and electrical function of the atria after the Maze procedure.
Table 1. Reported results of the Maze procedure

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<td>1998</td>
<td>30</td>
<td>57</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Pasic</td>
<td>1998</td>
<td>15</td>
<td>62</td>
<td>5</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Kalil</td>
<td>1999</td>
<td>61</td>
<td>49</td>
<td>-</td>
<td>3</td>
<td>93</td>
<td>80.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Kim</td>
<td>1999</td>
<td>75</td>
<td>48</td>
<td>5.6</td>
<td>0</td>
<td>100</td>
<td>90</td>
<td>2.7</td>
</tr>
<tr>
<td>Kosakai</td>
<td>2000</td>
<td>375</td>
<td>58</td>
<td>7.8</td>
<td>3</td>
<td>82</td>
<td>78</td>
<td>2.0</td>
</tr>
<tr>
<td>Cox</td>
<td>2000</td>
<td>299</td>
<td>-</td>
<td>-</td>
<td>51</td>
<td>28</td>
<td>98.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Arcidi</td>
<td>2000</td>
<td>99</td>
<td>61</td>
<td>8.6</td>
<td>21</td>
<td>70</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>Schaff</td>
<td>2000</td>
<td>221</td>
<td>56</td>
<td>-</td>
<td>23</td>
<td>66</td>
<td>85-90</td>
<td>1.4</td>
</tr>
<tr>
<td>McCarthy</td>
<td>2000</td>
<td>100</td>
<td>58</td>
<td>7.5</td>
<td>23</td>
<td>66</td>
<td>90</td>
<td>1.0</td>
</tr>
<tr>
<td>Albåge</td>
<td>2000</td>
<td>26</td>
<td>55</td>
<td>6.5</td>
<td>65</td>
<td>23</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>Jessurun</td>
<td>2000</td>
<td>41</td>
<td>49</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>Raanani</td>
<td>2001</td>
<td>47</td>
<td>68</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>75</td>
<td>4.0</td>
</tr>
<tr>
<td>Izumoto</td>
<td>2001</td>
<td>87</td>
<td>59</td>
<td>9.9</td>
<td>0</td>
<td>100</td>
<td>93</td>
<td>4.6*</td>
</tr>
</tbody>
</table>

Total 1476

*mortality during surgery and during the first postoperative year.

Prophylactic atrial pacing

The observation that a subgroup of patients with paroxysmal AF had predominantly vagally-induced AF, with relative bradycardia preceding the onset of AF (143), resulted in the hypothesis that atrial pacing may prevent AF. Coumel first tried this hypothesis in 1983 in a study of six patients with paroxysmal AF (143). In this study atrial pacing at a rate between 85 and 90/minute in combination with amiodarone was effective in reducing the number
of AF episodes. This study has been followed by others in which the effect of atrial pacing at different rates in patients with or without a clinical indication for pacemaker therapy has been studied (144-152). Atrial pacing has proved to be effective in reducing the number of paroxysmal AF episodes in patients with concomitant bradyarrhythmias such as sick sinus syndrome or AV block (144,151,152).

The mechanisms for this prophylactic effect of overdrive atrial pacing are unknown but have been proposed to be related to suppression of premature atrial contractions (PAC), elimination of post-PAC pauses, and decreased inhomogeneity in atrial refractoriness (153,154). Synchronous biatrial pacing, used in order to decrease the inter-atrial conduction delay, has been suggested to have advantages over single-site atrial pacing. In patients with inter-atrial conduction delay, biatrial pacing resynchronizes the electrical activity of the two atria, expressed as normalization of P-wave morphology and duration (155). However, in clinical studies, the effect of biatrial pacing has not been significantly better than single-site atrial pacing (145). To this date, there are no convincing data supporting atrial pacing as an effective prophylactic therapy for AF in patients without a conventional clinical indication for pacemaker therapy.
Aims of the thesis

1. Previous studies have demonstrated that the Maze procedure is effective in restoring sinus rhythm in patients with paroxysmal or chronic AF. The surgical procedure is, however, extensive with risk of complications. An improvement in quality of life can therefore not be taken for granted in patients undergoing the Maze procedure with the primary indication to alleviate symptoms of AF. The aim of the study was therefore to establish if quality of life was improved after the Maze procedure in patients with severely symptomatic AF.

2. During the Maze procedure several incisions are made in both atria with subsequent suturing, and both auricles are excised, which will result in scarring. This could hypothetically lead to a stiff and non-compliant atrial myocardium with an impaired transport function. Because the majority of patients operated with the Maze procedure have had permanent AF, no comparisons exist between the transport function before and after the operation. The aim of the study was therefore to assess if atrial size and transport function were affected by the Maze procedure and to explore the time-course of any such change.

3. Previous studies have demonstrated that heart rate variability can be used to estimate the autonomic modulation of the heart. During the Maze procedure several incisions are made in both atria, including a circular incision around the pulmonary veins that will possibly interrupt some of the autonomic nerves. The aim of the study was to assess if and in what respect heart rate variability was affected by the Maze procedure, with special emphasis on the autonomic balance, and to explore the time-course of any such changes. A further purpose was to explore if there were differences in HRV between patients with paroxysmal and permanent AF before the operation.

4. Small, observational studies have implied that atrial overdrive pacing can prevent recurrences of AF in patients with bradycardia. If the beneficial effect of overdrive atrial pacing in preventing AF recurrences can be also achieved in patients without bradyarrhythmias is unknown. The aim of the study was therefore to assess if atrial overdrive pacing can be used to prevent symptomatic recurrences of AF in a population of patients with drug-resistant, paroxysmal AF and no clinical indication for pacing.
Material and Methods

Subjects
Between February 1996 and February 2000 a total of 75 patients underwent the Maze procedure at University Hospital, Uppsala. The primary indication for cardiac surgery in all patients was severely symptomatic AF that could not be controlled by antiarrhythmic drugs. All patients gave informed consent.

Paper I included the first 49 patients that underwent the Maze procedure. In paper II and III a number of patients with concomitant diseases affecting the parameters studied were excluded. This resulted in a homogeneous study population but a smaller number of eligible patients. In paper II only patients with paroxysmal AF without any concomitant cardiac disease requiring additional cardiac surgery (except CABG) were included. A number of patients with paroxysmal AF were further excluded from this study due to AF at the time of the preoperative evaluation. In paper III only patients without associated diseases known to affect HRV were included. Unfortunately a number of common cardiac diseases affect HRV, such as ischemic heart disease, valvular diseases, congestive heart failure, thereby limiting the number of eligible patients in the study.

Table 2. The number of patients included in the papers and their background data

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENTS</th>
<th>MALE</th>
<th>AGE</th>
<th>DURATION</th>
<th>LONE AF</th>
<th>PREVIOUS OF AF</th>
<th>AA DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(number)</td>
<td>(%)</td>
<td>(years)</td>
<td>(years)</td>
<td>(%)</td>
<td>(years)</td>
<td>(number)</td>
</tr>
<tr>
<td>PAPER I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>80</td>
<td>52 (27-72)</td>
<td>8 (1-25)</td>
<td>80</td>
<td>5.0 (2-8)</td>
<td></td>
</tr>
<tr>
<td>PAPER II</td>
<td></td>
<td>71</td>
<td>59 (34-72)</td>
<td>16 (2-25)</td>
<td>76</td>
<td>4.8 (2-7)</td>
<td></td>
</tr>
<tr>
<td>PAPER III</td>
<td></td>
<td>88</td>
<td>51 (40-67)</td>
<td>11 (1-25)</td>
<td>76</td>
<td>4.9 (2-7)</td>
<td></td>
</tr>
<tr>
<td>PAPER IV</td>
<td></td>
<td>77</td>
<td>59 (30-78)</td>
<td>7.7 (1-16)</td>
<td>63</td>
<td>2.9* (1-4)</td>
<td></td>
</tr>
</tbody>
</table>

Previous AA drugs refer to antiarrhythmic drugs tried and found ineffective or with intolerable side effects.

* excluding beta-blocking agents, calcium antagonists and digitalis.
In paper IV patients with severely symptomatic paroxysmal AF were included at three study centers with recruitment beginning in May 1995 and follow-up ending January 2000. The only generally accepted non-pharmacological therapy for patients with severely symptomatic AF that did not respond to medical treatment was His-bundle ablation during the period that patients were included in paper IV. The reluctance of many patients to accept permanent pacemaker dependence following His ablation resulted in recruitment of several patients in paper IV referred to the hospitals as possible candidates for His-bundle ablation. The inclusion criteria were: at least two episodes of AF per month for the last three months, sotalol and one class I antiarrhythmic drug tried and found ineffective or intolerable, and symptoms severe enough that amiodarone or AV node ablation was considered. Patients with other arrhythmias were excluded, as were patients with significant cardiac disease. Despite the fact that patients with stable angina pectoris, congestive heart failure NYHA I-II, and hypertension were allowed to participate in the study, 63% of the patients had lone AF. The number of patients included in the different papers and some of their background data are given in Table 2.

Preoperative examinations of candidates for the Maze procedure
All potential candidates for the Maze procedure underwent diagnostic electrophysiological investigation to exclude triggering arrhythmias such as atrial flutter, atrial tachycardia, AV nodal reentry tachycardia, and concealed WPW-syndrome. A 24-hour Holter recording and an exercise test were performed to exclude sick sinus syndrome. A coronary angiogram was performed in all patients in order to detect concomitant silent myocardial ischemia. Furthermore, an echocardiographic examination was made to evaluate the left ventricular function and to exclude significant valvular disease. All patients finally accepted for Maze surgery underwent a specific echocardiographic examination according to the study protocol, and a quality of life questionnaire was handed out to them. Routine laboratory tests, including myocardial-specific markers (creatinine kinase-MB and troponin-t) and coagulation status (platelet count, antithrombin III, prothrombin complex, and activated partial thromboplastin time), were obtained according to clinical routine.

Routine procedures during surgery
Premedication with morphine-scopolamine was given the night before operation. After induction with fentanyl, thiopental and pancuronium, anesthesia was maintained with intermittent doses of fentanyl and isoflurane. To reduce postoperative bleeding, 2000 000 units of aprotinin were administered in the
heart-lung machine as a bolus followed by 500,000 units/hour as infusion during the operation. After systemic heparinization, cannulas were inserted in the aorta, in the superior and inferior vena cava, and the extracorporeal circulation was started in normothermia. The venous cannulas were snared, and the incisions and cryoablations were done in the right atrium on the beating heart. In patients with a permanent pacemaker, the electrodes were removed and the leads were cut in the superior vena cava. A patent foramen ovale or atrial septal defect was closed. Thereafter the patient was cooled to 32 degrees centigrade. Cardioplegic cannulas were placed in the aorta and coronary sinus. After clamping of the aorta, the heart was arrested by cold crystalloid cardioplegia – 700 ml given in the antegrade direction followed by 300 ml in the retrograde direction. Every 20 minute another 300 ml was given in the retrograde direction. Incisions and cryoablations were then done in the left atrium and the atrial septum. After closure of the left atrium, the aortic clamp was released and rewarming and deairing were commenced. The right atrium was closed on the beating heart. Temporary pacing wires were placed on the right atrium and the inferior surface of the left ventricle. The patient was weaned off cardiopulmonary bypass and decannulated. The heparinization was neutralized with protamine sulfate, drainage tubes were placed, and the sternotomy was closed. The complete Maze III procedure was carried out in all patients without any modifications.

Postoperative procedures
Temporary pacing in AAI mode was permitted during the early postoperative course before the return of a stable sinus node function. An aggressive diuretic regimen with furosemide and spironolactone was used to counteract fluid retention. After 2-4 days in the Intensive Care Unit the patients were taken to the ward in the Department of Cardiology. All patients were monitored with telemetry until they had a stable sinus rhythm, or in the case of sinus node dysfunction, until a permanent pacemaker was implanted.

Quality of life assessment
The term quality of life encompasses a very wide spectrum of human life, including health, social situation, and the economic and political situation and therefore no definition of the term exists. A pragmatic limitation of quality of life to health-related quality of life is used in medicine to assess physical and mental functioning and well-being related to different diseases and treatments. During the last decade there has been an increasing interest in measuring health-related quality of life because of awareness that traditional end-points such as
mortality and morbidity are in many situations not enough to assess and compare different treatments.

SF-36 (Short Form 36 questions) has been developed from the original questionnaire with 149 questions, and studies show sustained psychometric quality compared to the longer form (156). The questionnaire is composed of 35 questions divided into 8 scales (Table 3). One additional question evaluates changes in health and is outside the scales. The higher the number of levels within a scale the higher the precision of the scale (157).

**Table 3. Information about the SF-36 scales.**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Items (number of)</th>
<th>Levels</th>
<th>Lowest Possible</th>
<th>Highest Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>10 21</td>
<td>Limited a lot in performing all physical activities including bathing or dressing due to health.</td>
<td>Performs all types of physical activities including the most vigorous without limitations due to health.</td>
<td></td>
</tr>
<tr>
<td>Role-Physical</td>
<td>4 5</td>
<td>Problems with work or other daily activities as a result of physical health.</td>
<td>No problems with work or other daily activities as a result of physical health.</td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>2 4</td>
<td>Very severe and extremely limiting pain.</td>
<td>No pain or limitations due to pain.</td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>5 21</td>
<td>Evaluates personal health as poor and believes it is likely to get worse.</td>
<td>Evaluates personal health as excellent.</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>4 21</td>
<td>Feels tired and worn out all of the time.</td>
<td>Feels full of pep and energy all of the time.</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>2 9</td>
<td>Extreme and frequent interference with normal social activities due to physical or emotional problems.</td>
<td>Performs normal social activities without interference due to physical or emotional problems.</td>
<td></td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>3 4</td>
<td>Problems with work or other daily activities as a result of emotional problems.</td>
<td>No problems with work or other daily activities as a result of emotional problems.</td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>5 26</td>
<td>Feeling of nervousness and depression all of the time.</td>
<td>Feels peaceful, happy, and calm all of the time.</td>
<td></td>
</tr>
</tbody>
</table>
The answers obtained are transformed into scale scores, ranging between 0-100. The original US version of SF-36 has been translated into Swedish and the Swedish version is equivalent to the US version in quality (158). The SF-36 questionnaire was used in paper I because it is a generic instrument that is well validated, has high reliability, has been translated into Swedish, and normative data for the general Swedish population exist (159). The normative data available for the general Swedish population age 45-54 years were plotted in the figures for a rough comparison with the patients in the study. No strict matching with controls was done in the study because to achieve a good match not only factors such as sex and age are of importance but also education and social situation (159).

A research nurse, who informed the patient about the importance of answering all questions, handed the questionnaire to the patient before the operation. After the operation the questionnaires were sent to the patients before the follow-up visits.

**Echocardiography**

All 17 patients in paper II were examined by echocardiography before surgery and 6±1 months after the procedure. Twelve patients underwent a series of echocardiographic examinations during follow-up, at a mean time of 2±1, 6±1, and 24±3 months after surgery. Echocardiographic examinations were made according to a standard study protocol by experienced technicians, supervised by a clinical physiologist. They used a Hewlett Packard Sonos 1500, 2500, or 5500 instrument with a 2,5 MHz transducer and recorded the examinations on VHS videotapes. The examinations were later reviewed by one cardiologist (S.L). The echocardiographic examinations were not blinded to the researcher, but the results of previous measurements were not known at the time the later examinations were reviewed.

Values of maximal right and left atrial cavity areas were obtained by planimetry in the apical four-chamber view at the end of systole, defined as the last frame prior to mitral valve opening. Minimal left and right atrial cavity areas were obtained at end diastole at the time of the R wave on the ECG. The mean values were calculated from three to five consecutive beats. The atrial fractional area change (maximum area-minimum area/maximum area x 100) of the right and left atria was then calculated. Pulsed-Doppler echocardiography was used to assess the transmitral flow velocities from an apical four-chamber view with a sample volume from the tip of the mitral leaflets during diastole. Peak velocities of the early filling (E) wave and atrial filling (A) wave, as well as the deceleration time of the E wave, were
measured and averaged over three to five beats, and the E/A ratios were calculated.
Left ventricular systolic function was visually assessed and categorized as normal (LV-EF >0.50), slightly depressed (LV-EF 0.45-0.50), moderately depressed (LV-EF 0.30-0.45), severely depressed (0.15-0.30) and very severely depressed (<0.15).
The heart rates were derived from the three-channel ECG recording at each echocardiography examination.

Reproducibility was evaluated in 11 randomly picked examinations as the variability between a first and a second measurement at one recorded echocardiographic examination. Comparisons for reproducibility were made of the left and right atrial area fractional changes and transmitral Doppler E/A ratio. No statistically significant differences were found with the paired t-test or Wilcoxon’s matched-pairs test.

HRV analysis
Afferent stimulation of ANS, as part of reflex loops, results in sympathetic and/or parasympathetic nerve stimulation affecting the heart rate. These reflex loops have different reaction times, which results in rhythmic oscillations of the beat-to-beat interval of different frequencies (160). HRV, which does not actually measure the variability of the heart rate but rather the variability of intervals between consecutive heartbeats, is a non-invasive method for assessing the ability of ANS to modulate the heart rate (161). Changes in HRV can be due to changing function of the reflex systems, changing function of ANS, or changing ability of the sinus node to react to sympathetic or parasympathetic stimulation. Previous studies have shown that in individual patients or groups of patients HRV measurements were very stable over time (162).

There are two principally different ways of measuring HRV: time domain and frequency domain measurements (161).
Time domain analysis is based directly on the beat-to-beat intervals. The components most commonly measured are the mean RR interval (often designated NN = normal to normal), the standard deviation of all NN intervals (SDNN), the mean of the standard deviations of all NN intervals for all 5 minutes segments of the entire recording (SDANN), and the square root of the mean of the sum of the squared differences between adjacent NN intervals over the entire recording (RMSSD) (161).

Frequency domain analysis, also termed power spectrum analysis, breaks down the signal into its constituent frequency components and quantifies the variance or power of these components (161). For optimal reliability and reproducibility
of the spectral analysis, the heart rate signal must be properly pre-processed, as the values or samples in the beat-to-beat time series are not spaced at equal distances in time. There are different methods of making a power spectrum analysis. The method used in paper III was auto-regressive modeling (163), which provides smooth and easily interpretable spectral shapes, and a straightforward decomposition of the spectra into root components without the need for predefined spectral bands (161).

To secure high data quality, epochs with more than 4% of non-normal RR intervals were excluded from further analysis. For a tape to be included, a total of 16 hours, including at least 75% of the nighttime, had to be analyzable. The night was defined as the period between midnight and five AM. In paper III the power spectrum of the frequency domain was divided into different frequency bands as proposed by Bigger (164): the very low-frequency (VLF), 0.033-0.04 Hz (ms2); the low frequency (LF), 0.04-0.15 Hz (ms2); the high frequency (HF), 0.15-0.4 Hz (ms2); and the total power.

In addition, we calculated the ratio of LF to HF power. The HF component reflects respiratory sinus arrhythmia and is mainly related to parasympathetic activity (165-166), whereas the LF component is considered by some to reflect the sympathetic activity (166) and by others as a parameter that includes both sympathetic and parasympathetic nerve influences (165,167). However, if corrections are made for difference in heart rates, the LF component is considered to mostly reflect sympathetic activity (161). The LF/HF ratio was calculated to mirror the sympathovagal balance (168). Since the mechanisms underlying the VLF oscillations are not yet fully understood and the physiological correlate is unknown, VLF power was not used in our study. Several of the time domain and the frequency domain components correspond closely to each other. Mathematically, heart period variance, equal to SDNN squared, and total power are identical. However, in paper III we estimated total power by calculating the total power of successive 5-minute periods, and therefore both SDNN and total power were assessed in the paper. RMSSD correlates very strongly to HF power and SDANN correlates strongly to SDNN and therefore RMSSD and SDANN were not assessed in paper III (162, 169).

All patients planned for Maze surgery underwent unrestricted 24-hour Holter monitoring before the operation and at follow-up at 2±1 (mean±1SD) months and 7±1 months after the operation. A standard Del Mar Avionics three-channel tape recorder was used (Model 459, Del Mar Avionics, Irvine, California). The ECG signal was digitized and stored, using a commercially available PC-based system. The QRS complexes were initially classified as normal or non-normal by the Del Mar Model 563 StrataScan™ Holter Analysis System to exclude
artifacts and premature ventricular contractions. A QRS complex occurring with more than 20% prematurity compared to the preceding RR interval was classified as non-normal. All recordings were then visually scanned and the accuracy of the automatic classification was reviewed. Only normal RR intervals were used for the measurement of RR intervals; gaps in the time series were filled with values calculated by linear interpolation between the adjacent normal RR intervals.

Study design of paper IV
Digitalis and all class I and class III antiarrhythmic drugs except ineffective amiodarone were withdrawn after inclusion. After drug stabilization for two weeks, a run-in period of four weeks followed during which the number of ECG-documented symptomatic episodes of AF with duration < 30 seconds was assessed. The number of AF episodes during the run-in period (minimum 2) was later used to determine the length of the pacing phases. During the run-in period an echocardiographic examination was made to exclude significant valvular disease or cardiomyopathies. Previous studies have shown that atrial pacing reduces the frequency of AF in patients with sick sinus syndrome (144,151-152). Since we wanted to study the effect of pacing in patients without significant bradycardia, a 24-hour Holter ECG and a bicycle stress test were done during the run-in period besides taking a careful history to exclude sick sinus syndrome. The mean heart rate in the daytime during sinus rhythm was 68.7 bpm (range 52-85) in the included patients.

The study had a crossover design with three pacing phases (in patients with a high mean heart rate during run-in only two); OAO (no pacing), medium-rate overdrive pacing, and high-rate overdrive pacing (Figure 2). The pacing rate was based on the mean heart rate in the daytime during sinus rhythm during run-in + 10-19 bpm and 20-29 bpm respectively to assure a high proportion of pacing. The pacemaker programming was blinded to the patient. The primary endpoint of this study was the number of symptomatic and sustained episodes of AF, verified with ECG. The secondary endpoint was a comparison between medium-high and high-rate overdrive pacing.
Preentry visit (AA withdrawal)

Run in

PM-implant and Randomization

2-4 weeks

documentation of symptomatic PAF episodes

2 weeks

4 weeks

Study phases
4-12 weeks / phase

Cross-over

mHR + 10-19 bpm

mHR + 20-29 bpm

OAO (no pacing)

Cross-over

Figure 2. The overall design of study IV. The length of the different study phases depended on the number of PAF during the run in period. AA refers to antiarrhythmic drugs of class I, class III, and digitalis. The mHR refers to the mean heart rate in daytime during sinus rhythm.
Statistics
For the SF-36 scales General Health, Vitality, and Mental Health, it has been calculated that 30 patients is a sufficient number to detect a point difference of 10 over time within a group. For the other scales, 30 (and also 25) patients are sufficient to detect a point difference of 20 over time within a group. This is estimated based on an assumed alpha 0.05, two-tailed t-test, power 80% and an intertemporal correlation between scores of 0.60 (Cohen 1988).
In paper IV it was calculated that in order to detect a 50% reduction in the number of symptomatic AF episodes with a confidence of 95% and a power of 85%, alpha 0.05, 40 patients had to be included in the study.

In papers I-III all variables are presented as mean values ± one SD. Comparisons between groups were made with a two-tailed t-test. In paper III it was unclear whether the samples within the groups were normally distributed or not; therefore comparisons were also made with Wilcoxon’s signed ranks test. Since there were no differences in the levels of significance, only the results of the t-tests are presented. In paper IV it was clear that the numbers of AF episodes per week were not distributed normally among the patients; hence median values were used in the comparisons between programming phases. Wilcoxon’s signed ranks test was used for comparisons between the groups. Values of p less that 0.05 were considered significant.
Main results

Quality of life before and after the Maze procedure (paper I)

Before the Maze procedure the quality of life was markedly and significantly lower on all scales, except for bodily pain, than for the age-matched general Swedish population (Figure 3). A comparison between the group of patients with paroxysmal/persistent AF and patients with permanent AF revealed no significant changes in quality of life except for the variable physical functioning, which was lower for the patients with permanent AF. At the time of the study 37 patients had reached the 6-month follow up. Of these, data exist for only 30 patients, since 4 patients could not be followed because they lived abroad and the questionnaires of another 3 patients were not completed. The reason for the latter is unknown but none of the patients had refused to fill in the questionnaire.

Figure 3. Health-related quality of life before the Maze procedure assessed with the SF-36 (mean and 95% confidence interval. ◆ = Maze patients, △ = Swedish normal population age 49-54 years.
Abbreviations: PF = Physical functioning, RP = Role physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role emotional, MH = Mental health.
For 25 of the patients one year data also exist. The quality of life scores at 6 months after surgery compared to baseline had improved significantly on all variables except for bodily pain. The improvements in quality of life were maintained one year after the operation, with no significant changes between the SF-36 scores obtained six months and one-year after the Maze procedure, but a trend towards even higher scores. One year after the operation the SF-36 scores obtained were comparable to the average scores of the general Swedish population in the age group 45-54 years (Figure 4).

**Figure 4.** Health-related quality of life one year after the Maze procedure assessed with the SF-36 (mean and 95% confidence interval). ♦ = Maze patients, △ = Swedish normal population age 49-54 years.

Abbreviations: PF = Physical functioning, RP = Role physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role emotional, MH = Mental health.
**Atrial size and transport function before and after the operation (paper II)**

A decrease in the right and left maximal atrial size was observed at six months postoperatively compared to baseline: 14.0±3.2 versus 16.4±3.4 cm² (p=0.0008), and 15.4±3.4 versus 17.6±3.2 cm² (p=0.01) respectively. The fractional change in the right atrial area (maximum area-minimum area / maximum area X 100) decreased to 14.5±9.7 compared to 31.1±12 before the Maze procedure (p=0.004) and the left atrial fractional area change decreased to 19.9±9.1 compared to 36.3±9.1 before the Maze procedure (p<0.0001).

A detectable transmitral A wave, generally acknowledged as a sign of active atrial contraction, was found in all patients prior to surgery and in 15 out of 17 patients (88%) six months postoperatively. The transmitral peak A wave velocity decreased to 30±12 cm/s six months after surgery compared to 38±15 cm/s before surgery (p=0.03). In contrast, the transmitral E wave increased to 67±16 cm/s at six months after surgery compared to 52±16 cm/s before surgery (p=0.0001). The E/A ratio therefore increased from 1.6±0.9 before surgery to 2.5±0.9 at six months follow-up (p=0.0002).

![Figure 5](image)

**Figure 5.** The fractional area change ((max area-min area) / max area) of the left and right atrium before and 2, 6, and 24 months after the Maze procedure (mean and 95% confidence interval).

* p<0.05 versus baseline, all other changes non-significant
The deceleration time of the transmitral E-wave was $223\pm43$ at baseline and $216\pm37$ at six months ($p=0.4$). Twelve patients had a series of echocardiographic examinations postoperatively. The fractional atrial area change could be evaluated at all follow-up visits in 10 out of these 12 patients (Figure 5). One patient had poor image quality at one examination and one recording was missed. The E and A waves could be evaluated in 9 out of these 12 patients. Two patients were in nodal rhythm at one of the follow-up visits, and hence had no A wave, and one patient had a sinus tachycardia above 100 at one follow-up visit, making the E and A waves inseparable from each other. The E/A ratios for the patients serially examined postoperatively are shown in Figure 6. In two patients the A wave was not detectable at 24 months after the operation, and the A wave was therefore assumed to be zero. For these two patients the E/A ratio was not calculated and the figure is therefore based on seven patients.

Figure 6. The transmitral E/A ratio measured with pulsed Doppler technique before and 2, 6, and 24 months after the Maze procedure (mean value and 95% confidence interval). *$p<0.05$ versus baseline, ** $p<0.05$ versus 2 months after Maze surgery.
HRV before and after the Maze procedure (paper III)

A marked reduction in SDNN and the frequency domain components Total power, LF power, HF power was observed two months after the Maze procedure compared to the preoperative values (Figure 7). The LF/HF ratio decreased between the values obtained at baseline and those obtained two months after surgery (2.55±1.39 versus 1.22±0.92), indicating a proportionally greater reduction in LF power than in HF power.

Seven months after the Maze procedure SDNN and all frequency domain variables were still markedly reduced (Figure 7). Although there was a trend toward increasing values at seven months compared to those at two months, the difference did not reach statistical significance except for the Total power.

Figure 7. The power of different HRV components assessed during 24 hours before, and 2 months, and 7 months after the Maze procedure (mean value and 95% confidence interval).
The LF/HF ratio increased between two and seven months after the Maze procedure, but not significantly, and at seven months it did not differ significantly from the baseline value.
There was no significant difference between the mean RR intervals at baseline and after two and seven months of follow-up (905±200 ms, 752±106 ms, and 874±113 ms, respectively)
Seven months after the Maze procedure the SDNN, Total Power, LF, HF or the LF/HF measured did not differ significantly between the group of patients with paroxysmal AF and the group with chronic AF preoperatively.

Effects of overdrive pacing on the number of AF episodes (paper IV)
Of the fifty-one patients who started the run-in period, five patients developed persistent AF after withdrawal of antiarrhythmic drugs, two patients had sick sinus syndrome, and two patients had less than two episodes of AF during run-in and could therefore not be included. Of the 42 included patients, four developed persistent AF during the study, one developed unstable angina requiring CABG, and two refused to continue and were therefore excluded from further analysis. The results are thus based on 35 patients. The mean number of AF episodes during run-in was 9.4 (range 2-45). The atrium was paced 84% of the time during medium-rate overdrive pacing and 91% of the time during fast-rate overdrive pacing.
The number of symptomatic episodes of AF was significantly lower during medium rate overdrive pacing than during the control phase with no pacing (OAO), while the number of symptomatic episodes of AF during run-in and OAO did not differ significantly (Figure 8). The efficacy of medium-rate overdrive pacing was similar between the patient groups with different mean heart rates during the run-in period. The results of fast-rate overdrive pacing were very similar to those of the medium-rate overdrive pacing with a significantly lower number of symptomatic AF episodes during fast-rate overdrive pacing than OAO (Figure 9). Twenty patients were paced at both medium-rate overdrive and fast-rate overdrive with no significant difference in the number of AF episodes between the two pacing rates (0.97 AF/week versus 0.75 AF/week). There was an individual response to overdrive pacing, but for 17 patients a reduction of at least 50% in the number of symptomatic AF episodes was observed during medium rate overdrive pacing.
The adverse effects seen in the study were: three cases of minor scar infections, two cases of subclavian vein thrombosis, and two cases of early electrode dislocations.
**Figure 8.** The median number of ECG documented symptomatic PAF during the run-in, the OAO phase (no pacing), and medium high-rate (MR) overdrive pacing (mean heart rate + 10-19 bpm)

**Figure 9.** The median number of ECG documented symptomatic PAF during the run-in, the OAO phase (no pacing), and fast-rate (FR) overdrive pacing (mean heart rate + 20-29 bpm)
Discussion

The optimal treatment of AF is maintenance of sinus rhythm without any recurrences of AF. This goal is, however, accomplished with pharmacological therapy in only a minority of the patients, and the therapeutic alternative that remains is rate control (170). For the group of patients with drug-resistant AF with severe symptoms, a number of non-pharmacological therapies aiming at prevention or cure have been suggested. The papers included in this thesis evaluate two of these non-pharmacological therapies, the Maze procedure and overdrive atrial pacing.

In paper I, it was established that the patients selected for Maze surgery at our hospital reported a very low quality of life before surgery, regardless of whether they had paroxysmal or permanent AF. There are, to my knowledge, no reports on the quality of life in an unselected population of patients with AF. The health-related quality of life in our patients appeared to have been lower than that of 73 patients consecutive patients with paroxysmal AF (63). In that study, however, only patients with lone AF and not suffering from diabetes mellitus were included.

When the quality of life among our patients was compared with that in the normal Swedish population, the data could not be strictly matched. The quality of life data for the Swedish population are, however, divided into such narrow age ranges that it seemed acceptable to compare our data with the normative values.

A remarkable improvement in quality of life was observed in our study after the Maze procedure. This improvement may be related to alleviation of the symptoms secondary to AF, alleviation of symptoms related to side effects of pharmacological agents, or a placebo effect. The Maze procedure is a new and extensive therapy, and therefore a placebo effect due to the expectations of the patient and hospital staff can be anticipated. We believe that the placebo effect plays a minor role in the improvement of quality of life, because there was no change in quality of life between 6 months and one year after the operation. Whether the improvement in quality of life may be attributed more to the alleviation of symptoms of AF or to withdrawal of pharmacological drugs is, however, difficult to assess. One of the benefits of the Maze procedure is that the anticoagulation and antiarrhythmic drugs can be withdrawn after the operation, implying that it is justifiable to measure the combined effects of freedom of AF and reduced pharmacological therapy on quality of life.

The effects of the Maze procedure on quality of life are difficult to compare with the results of other non-pharmacological therapies for AF since the questionnaires used and populations studied vary. Earlier a custom-made quality of life questionnaire was commonly used to assess the efficacy of a tested therapy, but the results of these questionnaires should be interpreted with caution.
because the validity and reproducibility of these questionnaires have not been documented. During the last two decades a number of validated self-administered quality of life instruments have been developed, of which some have been translated into Swedish (159,171-173). None of these questionnaires has proved to be superior to the others. The SF-36 questionnaire was used because it is a generic instrument that is well validated, has high reliability, is translated into a Swedish version, and normative data for the general Swedish population exist (159).

The only other published study using SF-36 is one evaluating the effect of His bundle ablation on the quality of life in 159 patients with various supraventricular arrhythmias, including 22 patients with AF (174). In the patients with AF the quality of life improved significantly after the His bundle ablation, but the improvement obtained after ablation was far less than that obtained after Maze surgery, and the values did not reach those found in the general population. Lower baseline scores of SF-36 than in our population, however, indicate that co-morbidity was probably higher among the 22 patients undergoing His bundle ablation. Furthermore, the two therapies have different aims: heart rate control and limitation of symptoms versus cure of AF. Hence, the two studies cannot be properly compared. At present, there are no randomized trials comparing different non-pharmacological therapies for AF.

Although the Maze procedure is the only curative therapy for AF that is well documented, the effects on atrial transport function are still unclear. Left atrial contractions have been reported in 61-71% of patients with chronic atrial fibrillation after Maze surgery (175-178). There are no studies, however, comparing atrial contractions before, which requires sinus rhythm, and after the Maze procedure.

Pulsed Doppler technique measuring the transmirtal and transtricuspid inflow velocities has been the most widely used method for assessing atrial contractions before and after Maze surgery. The A wave is generally considered to represent the active atrial contraction (179). In a recent publication, the left atrial contraction was assessed with both transmirtal Doppler measurements and magnetic resonance imaging following the Maze procedure, and the correlation between the two methods was good (179). The size of the A wave or a quantitative analysis of atrial contractions was, however, not reported in that study. Measurements of intracardiac pressures by catheterization could be used to assess the true magnitude of atrial contraction, but this method was not considered feasible for repeated measurements.

The transmirtal inflow velocity assessed with Doppler technique is related to both the left atrial contraction and the left ventricular diastolic function (179). A significant change in the left ventricular diastolic function caused by the Maze
operation seems unlikely though, since no concomitant surgery was performed that could have affected the ventricles. Furthermore, in situations with impaired left ventricular diastolic function, as in restrictive myocardial disease, the deceleration time is markedly shortened (181), a feature that was not seen in our study. We therefore consider transmittal A wave assessment to be a good indirect method of estimating the force of the left atrial contraction. Since the absolute value of the inflow velocity is sensitive to the quality of the Doppler signal and the angle of the blood flow (179), the E/A ratio was added to estimate the proportion of ventricular filling by the atrial contraction (182).

Our observation that the A wave had decreased, the E/A ratio had increased and the fractional area change had decreased between baseline and the 2-month follow-up supports a reduced left atrial contraction. The continuous increase in the transmitral E/A ratio throughout the 24-month follow-up was due to a reduced velocity of the A wave and increased velocity of the E wave. The fractional area change of the left atrium also gradually decreased postoperatively, although this change was small and not statistically significant. The progressive increase in the E/A ratio was interpreted as a gradual decrease in the left atrial contraction.

During the Maze procedure, the posterior left atrium between the pulmonary vein orifices is electrically, and thus mechanically, isolated, thereby excluding approximately 30% of the left atrium from contributing to the transport function (184). It has further been hypothesized that this isolation of the posterior atrial wall in combination with a prolonged activation time of the left atrium can cause desynchronized atrial contractions (185). Moreover, interruption of atrial coronary arteries can result in impaired myocardial circulation (185). In an animal study comparing atrial function after different surgical procedures for chronic AF, the Maze procedure caused a significantly higher E/A ratio postoperatively compared to a novel surgical intervention, the radial approach (186). This finding strongly suggests that the increase in the E/A ratio seen after Maze surgery is caused by decreased atrial transport function due to the surgical procedure and not by open-heart surgery per se.

Our findings clearly contradict the observation in a study in which the A wave increased and the E/A-ratio decreased between 19±8 and 245±134 days after the Maze procedure (183). A possible explanation for the conflicting results is that all patients in that study had concomitant valve surgery, which probably affected both the atrial transport function and the ventricular diastolic filling pattern. This hypothesis is further strengthened by the results of another study (176), in which there were no differences in mean transmitral or tricuspid E/A ratios at repeated follow-up visits after Maze surgery in a mixed population of chronic and paroxysmal AF, some of whom underwent concomitant valve repair.
Although only a limited number of patients could be followed in our study, our findings are supported by a similar observation in another study including some patients with paroxysmal AF and sinus rhythm before surgery. In that study the transmitral E/A ratio increased from 1.7±0.8 before surgery to 4.2±1.2 after surgery in the 5 patients with paroxysmal AF before the operation (176).

If a progressive decline in atrial transport function can be confirmed by other studies, it raises concerns about the long-term effects of the Maze procedure because a decrease in the atrial transport function may have significant clinical implications, such as a risk of thrombus formation. At present, the magnitude of atrial contractions required to prevent thrombus formation is not known.

In paper III the HRV components expressing sympathetic and parasympathetic modulation, as well as the global HRV, were markedly reduced early after Maze surgery compared to the preoperative values. The HRV remained markedly decreased at seven months after the Maze procedure, indicating a long-lasting reduction in the autonomic modulation of the heart. Low HRV values have previously been reported after the Maze procedure, although these studies included patients undergoing concomitant mitral valve replacements and those with permanent AF (187). The effect of longstanding AF on HRV is unknown. Since the HRV values seven months after surgery in patients with paroxysmal AF did not differ from those in patients with permanent AF in our study, permanent AF by itself does not seem to influence HRV significantly. Increased autonomic modulation (toward normalization), observed late (often 12 months) after the Maze procedure in other studies on the basis of HRV, may be related to longer follow-up periods, larger populations, different surgical techniques, or to patient selection (186-188). Previous studies have not been able to assess HRV preoperatively which means that HRV changes induced by the Maze procedure and the effects on sympathetic and parasympathetic modulation have not been reported previously.

The reduction in HF power noted after coronary bypass surgery is thought to reflect reduced parasympathetic modulation of the heart (189). In contrast to what is observed after the Maze procedure, the HF power returns to the preoperative levels within 3 months following coronary bypass surgery (189). This difference in the recovery of parasympathetic modulation observed after the two different surgical procedures may be attributed to different mechanisms of parasympathetic reduction. The resection line enclosing all pulmonary veins during the Maze procedure results in a partial surgical interruption of the intramyocardial projections of the vagus nerve, which may be responsible for partial parasympathetic denervation of the heart. The same pattern of HF power as that seen after the Maze procedure has been reported following heart
transplantation and, moreover, no signs of parasympathetic reinnervation have been seen during the first two years after transplantation (190). The low LF power observed both early and late after the Maze procedure suggests that sympathetic denervation also occurs. This again is in concordance with the changes seen in heart transplant patients, in whom there were no signs of sympathetic reinnervation of the heart during the first year after transplantation, but a gradual recovery in the following four years (191). The result of the present study thus suggests a modulation of both the parasympathetic and the sympathetic activity, consistent with a denervation of the heart similar to that observed after heart transplantation. It cannot be excluded, however, that changes in the target organ, the sinus node, caused by the operation are responsible for the decreased HRV postoperatively. This mechanism seems unlikely because none of the patients has developed signs of sinus node dysfunction after the operation. Pharmacological stimulation with agonists and antagonists to the adrenergic beta-receptors and the cholinergic receptors before and after the Maze procedure would have been necessary to establish a sinus node unresponsive to autonomic stimulation.

Both in patients with myocardial infarction and in those with advanced congestive heart failure, a reduced SDNN has been found to be correlated to increased mortality (192-194). The impact of reduced HRV after the Maze procedure is most likely different, since the mechanism for the reduced SDNN is believed to be different. Instead one may speculate whether the denervation of the heart may be of importance for the efficacy of the Maze procedure in alleviating AF. In an animal model, ablation of parasympathetic nerves innervating the atria was effective in abolishing vagally mediated AF. A limitation of this study was that a majority of the patients were on beta-receptor antagonists after the Maze procedure. Such drugs may increase the SDNN and the HF power, and hence the LF/HF ratio (195-196). In this study both SDNN and the HF power were markedly reduced after the Maze procedure despite more frequent use of beta-receptor antagonists after the procedure than before. It is therefore unlikely that the use of beta-receptor antagonists would significantly have altered the results of this study.

In paper IV it was demonstrated that the number of symptomatic, sustained episodes of AF can be significantly reduced with single-site right atrial overdrive pacing compared to no pacing in patients without bradycardia and no other indication for pacing. Similar findings have been reported in a number of studies, randomized (144) and non-randomized (43,151-152), that demonstrated positive effects of atrial overdrive pacing on the number of AF episodes in patients with coexistent bradyarrhythmias. It is not clear, however, if the mechanism for initiating AF is the same for patients with and without bradycardia. The result of paper IV is in conflict with the results of the fairly
large PA3 study in which patients with paroxysmal AF, but without bradycardia, were randomized to DDIR pacing at a lower rate of 30 bpm, or DDIR pacing at a lower rate of 70 bpm (148). In this study there was no prophylactic effect of pacing on the end-points time to first and second recurrence of AF. The reasons for the conflicting results could be an insufficient overdrive pacing rate and a lower proportion of atrial pacing in the PA3 study than in our study. The different end-points may also explain the different outcomes of the two studies. The use of symptomatic episodes of AF as the end-point in the study better correlates to the goals of treatment for paroxysmal AF, but there is a possibility that overdrive pacing renders some of the AF episodes asymptomatic. The true reduction in AF episodes or time in AF has not been measured in either this study or any previous studies.

The clinical relevance of a median reduction in symptomatic AF episodes by 50% is not known, but we do not consider the effect strong enough to recommend overdrive pacing in patients with paroxysmal AF without other indications for pacing. There was a remarkable difference in the results of overdrive pacing between the individuals in the study. This difference was not correlated to the baseline mean heart rate. The patient population in paper IV had an advanced AF disease with long AF duration and frequent episodes of AF. It might be that overdrive pacing is more efficacious in patients with a shorter history of AF and less atrial remodeling. Further evaluation of these patients should aim at finding characteristics identifying responders to pacing.
Conclusions

Patients with severely symptomatic AF who are treated with the Maze procedure report a significant improvement in their quality of life 6 months after the operation. This improvement is maintained at the 1-year follow-up. The quality of life measured at 6 months and 1 year after the operation is comparable to that of the general Swedish population. This study thus establishes that alleviation of AF is accompanied by an improvement in quality of life by the Maze procedure.

The size of the left and right atrium decreases after the Maze procedure compared to before the operation. The atrial transport function is decreased early after the Maze procedure compared to before the operation. There is a progressive decline in the atrial transport function over a period of 24 months following the Maze procedure. The impaired atrial transport function may imply a risk of thromboembolic complications.

There is a pronounced and long-lasting decrease in global HRV and HRV components representing sympathetic and parasympathetic nerve modulation after the Maze operation. This finding is consistent with partial denervation of the heart. The clinical implications of these findings are unknown.

The number of symptomatic episodes of AF can be significantly reduced with overdrive single-site right atrial pacing in a population with no other indication for pacing. The prophylactic effect was not correlated to the mean heart rate before pacing. The individual response to overdrive pacing was very diverse in our study and future studies should aim at identifying responders.
**Future perspectives**

Our studies show that the Maze procedure, besides a very high success rate in alleviating AF, improves the quality of life of the patients but has substantial effects on atrial transport function and the autonomic innervation of the heart. These effects are not simply negative side effects but may well contribute to the efficacy of the operation. The long-term effects are, however, not known and need to be clarified.

Since the development of the Maze procedure, ectopic beats in the pulmonary veins have been identified as triggers for AF in some patients, which has generated a growing interest in ablation techniques for AF. Although the results of these ablation techniques are very promising, ablations have mainly been performed in patients with paroxysmal AF. Furthermore, there seems to be a group of patients that are non-responders despite several ablation sessions. I therefore believe the Maze procedure still has a place in the treatment of AF in the following situations:

- Patients with severely symptomatic paroxysmal or persistent AF where pulmonary vein ablation has been unsuccessful.
- Patients with symptomatic permanent AF undergoing cardiac surgery for concomitant cardiac diseases.
- Patients with permanent AF undergoing mitral valve repair because anticoagulation can be avoided following Maze surgery with presumably less bleeding complications.

The overall response to single-site overdrive atrial pacing was moderate but the individual response was remarkably diverse. Further evaluation of these patients should aim at identifying responders to pacing.
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