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THE BURDEN OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is defined by irregular RR intervals and absence of P-waves on the electrocardiogram (Figure 1). Frequency of atrial activation is highly variable and can reach 300 beats per minute, with irregular conducted ventricular rates up to 200 beats per minute.1

AF is the most common arrhythmia in the world. In the Netherlands the overall prevalence of AF is 5.5%, with a higher incidence in older patients. There is a lifetime risk of 22-24% of developing AF after the age of 55 years.2 AF results in frequent hospitalizations and in-hospital procedures such as electrical cardioversion and ablation procedures. The costs of AF were estimated to be € 583 million in the Netherlands in 2009.3 This accounted for 1.3% of healthcare expenditure.3 It is estimated, using population projections from the Netherlands and large international cohort studies, that the prevalence of AF will have doubled in 2060.4–7 Such an increase is important as AF is related to debilitating morbidity and mortality, such as an increased risk of thromboembolic stroke.8,9

Figure 1. – Electrocardiographic tracings showing (A) a tracing with sinus rhythm with clear P-waves (black arrow), representing organized atrial activation. Below (B) a typical example of atrial fibrillation showing irregular ventricular rhythm with no clear P waves.

CLINICAL PRESENTATION OF ATRIAL FIBRILLATION

The clinical presentation of patients with AF is diverse. Patients can be asymptomatic, so called “silent AF”. However, a majority of the patients presents themselves at the outpatient clinic with complaints of palpitations, chest pain, dyspnea and decreased exercise tolerance. The current classification of AF is based on the duration of the episodes. Patients with paroxysmal AF have short episodes of AF that usually terminate spontaneously within 48 hours to 7 days. Patients with persistent AF have longer episodes of the arrhythmia, that do not terminate spontaneously and may last for more than 7 days. Finally, patients with permanent AF perpetually have AF, with little or no episodes of sinus rhythm.1 It is important to note that the current AF classification is not based on underlying pathophysiology, but purely based on the clinical presentation of the arrhythmia.
RISKS OF ATRIAL FIBRILLATION

Independent of the presentation of the disease, AF can result in a high ventricular rate. In patients with cardiac comorbidities this can lead to hemodynamic instability, requiring immediate treatment. Otherwise, a continuously high ventricular rate can result in acute decompensation and on the long term in a tachycardiomyopathy. This is a dilated cardiomyopathy without any signs of structural heart disease, that is potentially reversible when the ventricular rate is normalized.10

However, the most important complication of AF is the increased risk of thromboembolic stroke.9 The exact mechanism is not completely elucidated, however, due to the high atrial rate the atria cannot effectively contract which results in a ‘functional atrial standstill’ and an increased risk of blood coagulation. Otherwise, due to changes in the atrial myocardium with AF, a pro-thrombotic state is induced.12 The majority of these thrombi are located in the left atrial appendage.11 The risk of stroke due to AF can be estimated by using several factors such as congestive heart failure, hypertension, age, diabetes, prior thromboembolic events, vascular disease and gender.13 The incidence of stroke can be reduced with vitamin K antagonists such as warfarin or coumarins.14,15 However, these drugs have many drug interactions and require intensive laboratory monitoring and regular dose adjustment to be in the therapeutic range. Novel direct oral anticoagulation drugs such as dabigatran (thrombin inhibitor), apixaban, rivaroxaban and edoxaban (factor Xa inhibitors) are non-inferior to vitamin K antagonists and do not require intensive monitoring. They are therefore an attractive alternative.16–19

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

A single pathophysiological mechanism may occasionally play a major role in the occurrence of AF, such as postoperative AF or familial AF. In these types of AF inflammation or gene dysfunction in ion or gap junction channels bring about the arrhythmia.20,21 More often, AF is the result of the accumulation of changes to the atria due to aging, obesity or comorbidities such as diabetes, hypertension and sleep apnea.1 It can therefore be considered in most cases as an expression of underlying cardiovascular disease.

AF is often initiated from ectopic firing of cells in the pulmonary veins22, but other sources of atrial ectopic activity such as the left atrial appendage have been described.23 Ectopic activity can trigger reentry in the atrium.22 However, to sustain reentry a suitable substrate has to be present. Depending on structural characteristics of the atrium, such as atrial dilatation and fibrosis, the arrhythmia can be maintained.24 Interestingly, AF itself induces electrical, autonomic and structural changes, that remodel the atrium (Figure 2). These changes further facilitate the initiation and maintenance of AF, there-
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Figure 2. – Schematic summary of autonomic, electrical and structural remodeling of AF. Examples of changes occurring during AF in the atria in electrophysiological characteristics, structural properties and autonomic nervous innervation.

APD: action potential duration, AF: atrial fibrillation, ERP: effective refractory period

fore "AF begets AF". This remodeling explains the time course of the disease, which is characterized by a progression from short episodes of self-terminating AF to, ultimately, permanent AF.

ELECTROPHYSIOLOGICAL MECHANISM OF ATRIAL FIBRILLATION

AF has a complex electrophysiological mechanism that is not completely elucidated. Currently, two hypothesis are commonly used to explain the electrophysiological observations during AF (Figure 3). The multiple wavelet hypothesis was first postulated by Moe based on findings in a computer model of AF. The multiple wavelet hypothesis assumes that AF is maintained by small reentrant wavelets that wander chaotically through the atrium and continuously create new wavelets or break up due to conduction block or fuse with each other. Multiple wavelets were first observed in animal models by the group of Allessie. A second hypothesis postulates the existence of stable rapidly firing foci or reentry circuits giving rise to fibrillatory conduction. Reentry circuits, known as rotors, may be the underlying driver of AF. The finding of rotors in patients with AF by Narayan et al. provides novel insight into this hypothesis, as these investigators were able to ablate the rotors with catheter ablation and reduce recurrences of AF. However, due the heterogeneity of the underlying disease of AF different mechanisms might be present in certain types of AF. Additionally, both hypotheses may simultaneously underlie the mechanism of AF. Nevertheless, the multiple wavelets hypothesis and the rotor hypothesis both depend on either anatomical or functional re-entry circuits.
Re-entry relates to the wavelength of activation, which is the mathematical product of conduction velocity and refractory period. Therefore electrophysiological properties of the atrium that affect either conduction velocity or refractoriness, as well as structural characteristics of the atrial myocardium that determine the pathlength of activation determine the reentrant process causing AF.

AUTONOMIC MODULATION OF ATRIAL FIBRILLATION

An important modulator of the electrophysiological characteristics of the atrium is the autonomic nervous system. From the first descriptions of AF, the autonomic nerve system (ANS) was identified as an important trigger of AF. Historically, a clear distinction was made on basis of Holter recordings between vagal AF, preceded by slowing of the heart rate before onset of the arrhythmia and adrenergic AF, preceded by an increase in the heart rate before onset and usually occurring in patients with heart disease. However, a clear distinction between vagal or adrenergic AF is clinically not always possible, and in the majority of cases no clear provoking vagal or adrenergic momentum can be identified. However, although a clear clinical classification in patients is not possible, experimental in vitro, animal and human studies have shown that several specific actions of the autonomic nervous system can be arrhythmogenic. In animal studies, stimulation of the autonomic nervous system results in ectopic firing from the pulmonary veins and can initiate AF. In AF, specifically the parasympathetic nervous system is involved in the initiation and perpetuation of the arrhythmias. Parasympathetic stimulation results in release of acetylcholine, the main parasympathetic neurotransmitter, that results in a decrease in action potential duration through stimulation of the inward K⁺ current via...
Several aspects of the influence of the autonomic nervous system on the initiation and perpetuation of arrhythmias, in particular AF, will be discussed in this thesis.

**MANAGEMENT OF ATRIAL FIBRILLATION**

The management of AF consists of three important principles: thromboembolic risk reduction, arrhythmia management and cardiovascular risk factor reduction. Arrhythmia management and reduction of symptoms can be achieved with either rate control or rhythm control. Rate control aims to control the ventricular rate in patients with AF. Rhythm control aims to achieve sinus rhythm. There is no preference for either strategy, as none is superior to the other in regard to mortality. Yet, maintenance of sinus rhythm theoretically might be superior, as this is the normal cardiac rhythm. Indeed, population studies have observed that rhythm control reduces the progression of the disease to permanent AF. The non-superiority of rhythm control might be due to the side effects of the currently available anti-arrhythmic drugs. Many of the anti-arrhythmic drugs currently used in patients with AF also have pro-arrhythmic effects. Otherwise, many anti-arrhythmic drugs are contraindicated in certain populations of patients, such as flecainide in patients with ischemic heart disease or sotalol in patients with decreased renal function. Of note, the major randomized studies have not incorporated invasive treatment strategies for AF such as pulmonary vein isolation, which might increase the effect of rhythm control. Fortunately, in the majority of the patients symptom relief can be achieved with rate control and rhythm control. Nevertheless, a minority of the patients have debilitating symptoms from AF, for which invasive treatment might be indicated.

**INVASIVE TREATMENT OF ATRIAL FIBRILLATION**

Invasive treatment options of AF have been limited before the 21st century. The surgical Maze procedure described by Cox et al. was the first surgical AF treatment available. In this procedure the atrium is cut and sewed to create electrically isolated areas of atrial tissue to prevent development of macro-reentrant circuits. Experimentation with different ablation modalities such as cryo-ablation and radiofrequency ablation have made this procedure more accessible. The most recent iteration of this surgical maze procedure, the Cox-Maze IV, has a high success rate in preventing recurrence of AF with up to 78% of the patients free from AF and anti-arrhythmic drugs at one year. However, these procedures are invasive, technically challenging and associated with a mortality of 2-4% and morbidity such as postoperative bleeding in 4-5% and pacemaker implantation in 5-6% of patients.
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In a landmark study by Haissaguerre et al. the authors ablated ectopic foci originating from the pulmonary veins that triggered AF in patients with paroxysmal AF.\textsuperscript{22} The ablation of the foci in the pulmonary veins resulted in freedom from AF in 62\% of patients after 8 months follow up.\textsuperscript{22} The discovery that AF was frequently initiated from the pulmonary veins was the basis of pulmonary vein isolation with catheter ablation (Figure 4).\textsuperscript{54,59} Although pulmonary vein isolation is widely advertised, success rates are moderate with a single procedure success rate of 57\% after a mean follow up of 14 months in mainly paroxysmal AF patients.\textsuperscript{53} Most patients needed multiple procedures to achieve a success rate of 71\%.\textsuperscript{53} Patients have recurrences of AF due to the fact that the ablation lines of the pulmonary vein isolation are not always complete.\textsuperscript{54} Alternatively, there are other foci that can initiate AF, such as ectopic foci in the left atrial appendage.\textsuperscript{23} The unsatisfactory success rate of pulmonary vein ablation, especially in persistent AF, has stimulate the search for novel ablation targets. Substrate modulation of AF by ablation of additional atrial lines or ablation of areas of complex fragmented electrical electrograms ('CAFE’s) resulted in reduced recurrences of AF.\textsuperscript{60} However, a recent randomized trial in 589 patients with persistent AF comparing pulmonary vein isolation to pulmonary vein isolation with additional atrial ablation and pulmonary vein isolation plus ablation of endocardial electrograms showing complex fractionated activity, showed similar results in all three groups.\textsuperscript{61} In patients with pulmonary vein isolation alone, 59\% were free of AF after 18 months compared to 49\% of patients with pulmonary vein isolation and complex atrial electrogram ablation and 46\% of patients with pulmonary vein isolation and additional ablation lines.\textsuperscript{61} Novel strategies aim at identifying electrophysiological targets of AF. Focal impulse and rotor ablation by electrophysiological mapping of foci and rotors during AF appear promising.\textsuperscript{30} Otherwise, autonomic modulation through target ablation of the components of the cardiac autonomic nervous system appears to be successful and will be discussed in this thesis.\textsuperscript{38}

Simultaneous to these developments in endocardial catheter ablation, the principles of pulmonary vein isolation have also been applied epicardially by cardiac surgeons. A minimal invasive pulmonary vein isolation is a surgical procedure creating epicardial pulmonary vein isolation through a thoracotomy or totally thoracoscopically.\textsuperscript{62,63} This combination of surgical and electrophysiological expertise has created new hybrid ablation strategies that will be discussed in this thesis.

**UNANSWERED QUESTIONS**

As summarized above the etiology and treatment of AF is complex and many unanswered questions remain. In this thesis the following issues will be addressed:

1) What are the options for invasive autonomic modulation in cardiac arrhythmias
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2) What is the role of interstitial fibrosis of the human atria on conduction properties in patients with AF

3) How does ganglion plexus stimulation affect the electrophysiological properties of the atrium during sinus rhythm in patients with AF.

4) What is the effect of parasympathetic stimulation on conduction characteristics in the fibrotic atrium of patients with AF.

5) What are the current results of minimal invasive surgery using radiofrequency ablation?

Figure 4. – Anatomical representation of pulmonary vein isolation. The inside of the atria and ventricles are shown from an anterior view into the heart. The yellow dashed line is the area of the pulmonary vein isolation. Pulmonary vein isolation is the basis of invasive management of atrial fibrillation, either through catheter ablation or surgical ablation. This figure is adapted from Krul et al.59
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6) What are the results of thoracoscopic pulmonary vein isolation and ganglion plexus ablation using extensive epicardial electrophysiological guidance.

7) What are the results of extensive electrophysiological measurements either endocardially or epicardially in thoracoscopic pulmonary vein isolation in AF patients with enlarged left atria and/or earlier ablation procedures.

We use a translational approach to assess the role of the autonomic nervous system in the pathophysiology of AF. In patients with AF we performed thoracoscopic pulmonary vein isolation using epicardial electrophysiological guidance and performed autonomic modulation. We peri-procedurally investigated the electrophysiological properties of the atrium during autonomic modulation. We subsequently performed experiments on amputated tissue of the left atrial appendage of these patients to identify the fibrotic substrate and the effect of autonomic modulation of this substrate. Furthermore, we monitored these patients intensively to determine the outcome of thoracoscopic surgery and autonomic modulation in specific groups of patients.

OUTLINE OF THE THESIS

The parasympathetic or sympathetic nervous system can trigger or maintain episodes of atrial and ventricular arrhythmias. Chapter 2 reviews the role of the autonomic nervous system in atrial and ventricular arrhythmias. Furthermore, novel interventions targeted at the different components of the autonomic nervous system are described. Part One of this thesis addresses the role of atrial fibrosis and the autonomic nervous system in the pathophysiology of human AF. The effect of the human fibrotic substrate on electrophysiological properties of the atrium has not been studied in detail. In Chapter 3, we investigate the influence of the atrial fibrotic substrate on conduction properties of patients with AF. The fibrotic substrate of AF consists of depositions of extracellular matrix proteins like collagen from fibroblasts. The influence of fibrosis on conduction characteristics has not be entirely elucidated. Human AF is complex and a multitude of mechanisms contribute to the occurrence of AF. In Chapter 4 we investigate the effects of autonomic nerve stimulation on atrial conduction characteristics in patients with AF during thoracoscopic surgery. In this study local stimulation of both sympathetic and parasympathetic nerves was performed to assess the influence on sinus node frequency and local atrial conduction characteristics in patients with AF. To further investigate the observed effects of parasympathetic nervous system stimulation, in the fibrotic substrate of patients with AF local superfusion of acetylcholine was performed on excised left atrial tissue. We performed high resolution optical mapping to investigate the effects of vagal stimulation on conduction properties. The results of this study are reported in Chapter 5.
In Part Two of this thesis we continue with a focus on the treatment of AF. Minimal invasive pulmonary vein isolation is a novel treatment option for patients with AF. In a systematic review, in Chapter 6, we review published papers and investigate the first results of this treatment modality. In the Academic Medical Center of Amsterdam a variation of this procedure was developed. Whilst the surgical technique is similar to that reported in the majority of the studies, we performed extensive epicardial electrophysiological measurements of ablation lines during the thoracoscopic pulmonary vein isolation. Additionally, due to the epicardial approach of thoracoscopic surgery the autonomic nervous system (ganglion plexus, located within the epicardial fat pads) can be targeted, besides the electrical isolation of the pulmonary veins. The first results of this procedure are reported in Chapter 7. Since thoracoscopic surgery was first reported in 2005, many small studies have been performed with variations of the original procedure. Finally in Chapter 8, we performed an analysis on two patient cohorts who underwent either a fully epicardial approach or hybrid epicardial/endocardial approach with electrophysiological measurements. The patients in this analysis consists of a challenging population of patients with a failed previous pulmonary vein isolation and/or enlarged left atria. We report the safety of electrophysiological measurements and the outcome in these patient categories.

Finally we conclude this thesis with a summary in Chapter 9 in English and Chapter 10 in Dutch. Future directions for research of the pathophysiology of the autonomic nervous system in AF and the surgical treatment of AF will be discussed.
REFERENCES

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