Autonomic and surgical substrate modulation of atrial fibrillation
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Chapter 9

Summary and discussion
Atrial fibrillation (AF) is a complex arrhythmia, and results from multiple pathophysiological mechanisms. In recent years computer models, animal models and patient studies have shed light on different pathophysiological pathways. However, an integration of the results of these different models is often difficult due to the inherent limitations of each model. Innovative laboratory techniques such as optical mapping and novel treatment options create new opportunities for translational investigation of AF. The aim of this thesis was to study the role of autonomic nervous system in the pathophysiology of AF in the remodeled human atrium and to investigate minimal invasive surgery including autonomic modulation as a treatment of AF. In the introductory chapter 1 we give a general introduction into AF. We discuss the high burden of AF on general health care. Furthermore we describe the multi-factorial origin of the arrhythmia. We review the main objectives in the treatment of AF, which is largely aimed at reducing risks and symptoms. Finally, we discuss the different treatment strategies and invasive treatment options.

**Autonomic modulation of atrial and ventricular arrhythmias**

In chapter 2 we review the contribution of autonomic nervous system in the initiation and modulation of atrial and ventricular arrhythmias. Anatomical studies have revealed that the intrinsic cardiac autonomic nervous system consists of a network of interconnected nerves of both the parasympathetic and sympathetic nervous system on the atria and ventricles. The parasympathetic nerve fibers branch out from by the vagal nerve and the sympathetic nervous system derives from the stellate ganglion. The main function of the autonomic nervous system is regulation of heart rate and AV-nodal conduction. However, enhanced activity the parasympathetic and sympathetic nervous system can exert arrhythmogenic electrophysiological effects on atrial myocardium and the pulmonary veins. Otherwise, in the ventricle the sympathetic nervous system plays a more dominant role in arrhythmogenesis. Furthermore, we highlight novel methods to clinically identify the cardiac autonomic nervous system with imaging modalities and electrophysiological mapping. Identification of autonomic nervous system activity is possible with nuclear imaging, specifically $^{123}$MIBG-imaging. This technique may provide further insight in mechanisms and treatment targets. $^{123}$MIBG-imaging lacks the resolution for assessment of local atrial innervation and denervation and is therefore primarily used in the setting of ventricular arrhythmias. However, atrial effects of the intrinsic autonomic nervous system can be identified through stimulation and mapping of the ganglionic plexuses. Once reliable identification of the intrinsic autonomic nervous system becomes possible and the optimal treatment target and peri-procedural endpoints of autonomic nervous system modification are defined, clinical studies on modifying the
autonomic nervous system may open an entirely new stage for treatment of arrhythmias. We discuss autonomic modulation of the different components of the intrinsic and extrinsic autonomic nervous system in treatment of atrial and ventricular arrhythmias. Ablation of ganglion plexus shows promising results for the treatment of AF. New invasive treatment options aimed at the extrinsic cardiac autonomic nervous system, such as low level vagal stimulation with an extracardiac neural stimulator or renal denervation aimed at ablation of the sympathetic plexus near the renal arteries, provide interesting future treatment possibilities both for AF and ventricular arrhythmias. However, autonomic modulation of the extrinsic cardiac nervous system is invasive and associated with the risk of complications. Further clinical studies on autonomic modulation may not only improve the outcome of such procedures, but may also advance our understanding of how the autonomic nervous system interacts with the atrial and ventricular myocardium to cause cardiac arrhythmias.

PART I: THE ROLE OF ATRIAL FIBROSIS AND THE AUTONOMIC NERVOUS SYSTEM IN THE PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

In humans many different pathophysiologic mechanisms interact with each other that may result in AF. Furthermore, AF itself induces changes in electrophysiological properties of the atrium, and in the structure of the atrium and in autonomic innervation. It is unknown how this remodeling of the atrium influences already established mechanisms of AF. Both interstitial fibrosis and the autonomic nervous system play a substantial role in AF and have been extensively investigated as separate mechanisms. Interstitial fibrosis is associated with AF and creates an underlying substrate for AF. However, with drugs and progressing age the effects of the autonomic nervous system also changes. How these mechanisms interact and influence each other is not well known. Animal studies and computer model studies are essential in testing observations from human data to unravel the underlying isolated mechanisms. A major limitation of these models is that they cannot account for the complexity of the underlying disease in humans. Otherwise, human studies lack the possibility of a strictly controlled experimental setting. Therefore, the integration of these results and the confirmation of findings of experimental studies in clinical studies and vice-versa is vital in unraveling the complexity of human AF.

The fibrotic substrate of human atrial fibrillation

In patients with AF substantial atrial fibrosis is found, which is an important component of the arrhythmogenic substrate of AF. Interstitial fibrosis has direct and indirect arrhythmogenic effects. Direct fibroblast-cardiomyocyte coupling results in an increased
passive electric load to the cardiomyocytes, which can be arrhythmogenic in experimental studies.\textsuperscript{15} In particular, myofibroblasts, distinct fibroblasts that differentiate in response to pathological stimuli, couple directly with cardiomyocytes and contribute to extensive fibrotic remodeling.\textsuperscript{16} Fibrosis can become arrhythmogenic by increasing the extracellular matrix collagen content, separating atrial myocytes, and by increasing the length of activation pathways.\textsuperscript{17} The effect of the quantity and the structural organization of fibrosis on atrial conduction abnormalities in man are unknown. In chapter 3 we investigated the amount and organization of interstitial fibrosis and examined the effect of interstitial fibrosis on conduction characteristics in 35 left atrial appendages from patients with AF. We observed that the amount of fibrosis was unrelated to conduction velocity or patient characteristics. However, longitudinal conduction velocity was higher in left atrial appendages with thick compared with thin interstitial collagen strands, consistent with separation of myocardial fibers. Thick interstitial collagen strand were more frequently present in persistent AF patients. Local transverse conduction was not affected by these fibrotic strands, but activation delay was present in these preparations. Additionally, areas of activation block occurred, leading to zig-zag conduction. More pronounced slowing of conduction was observed after short-coupled stimuli. Short-coupled stimuli induced lines of conduction block, which were absent under baseline stimulation (functional lines of conduction block). Fibroblasts were present throughout the left atrial appendage and were associated with the presence of thick interstitial collagen strands. Myofibroblasts were not detected in the atrial appendages from these patients. Our observations show that the organization of interstitial fibrosis rather than the amount of fibrosis was associated with conduction changes in the left atrial appendage. These changes may result in a heterogeneity of conduction, caused by propagation of the activation front around inexcitable barriers. Thus, the occurrence of unidirectional conduction block and re-entry provides an arrhythmogenic substrate for both the induction and the maintenance of AF.

\textbf{Modulation of conduction by the autonomic nervous system in human atria}

Both atria are covered by small parasympathetic and sympathetic nerves fibers.\textsuperscript{2,3} Ganglionic plexus represent conglomerations of autonomic nerve fibers and ganglia, located on the right and left atrium, predominantly around the pulmonary veins.\textsuperscript{2} The effects of ganglion plexus stimulation, and thus autonomic stimulation, on atrial conduction characteristics in patients with AF are unknown. Conduction changes might increase the arrhythmogenic substrate in patients with AF induced remodeling. In chapter 4 we describe the effects of high frequency stimulation of the anterior right ganglion plexus during sinus rhythm on rate, AV nodal and atrial conduction properties in 25 patients undergoing thoracoscopic surgery for AF. During surgery the anterior right ganglionic plexus is stimulated at 16 Hz, with incrementing pacing output from 1 to 2 and 5 mA. From
the right atrium or right pulmonary vein epicardial electrograms are recorded using a 48-point electrode. From these electrograms activation times are determined, activation maps are created and conduction characteristics assessed. In these patients, the sinus-node response with a short-lasting progressive decrease in rate at increasing output of high frequency stimulation. The sinus node response is most likely mediated by a short lasting parasympathetic response. AV-nodal conduction is unchanged following high frequency stimulation of the ganglion plexus. Intra-atrial conduction and local conduction times and the inhomogeneity of conduction of atrial and pulmonary vein myocardium are influenced by high frequency stimulation, mediated by either a parasympathetic or sympathetic response or both. Contrary to changes induced by high frequency stimulation on sinus rhythm frequency, these changes persist during subsequent stimulation attempts. Local activation times either increase or decrease depending on the presence of beta-blocking agents; activation times increase in the majority of patients with beta-blocking drugs. This implies that the parasympathetic nervous system stimulation might induce conduction slowing in patients with AF. Our study supports the notion that ganglion plexus ablation may contribute to decrease the arrhythmogenic substrate for AF not only by the prevention of triggered activity, but also by the prevention of autonomic modulation of atrial conduction.

In chapter 5 we further investigate the influence of the parasympathetic nervous system on conduction in patients with AF. Left atrial appendages are amputated during thoracoscopic surgery for AF. Activation times are measured with high resolution optical mapping. Conduction times are calculated from activation maps and conduction block is quantified before and after superfusion with acetylcholine, the major parasympathetic neurotransmitter. In this study, acetylcholine increases dispersion of local activation times during the presence of short-coupled extra stimuli compared to control experiments. Additionally, acetylcholine increases the number of lines of conduction block. Conduction block is more often viewed with short-coupled extra stimuli near the effective refractory period. Furthermore, changes in activation direction occur exclusively in atrial appendages exposed to acetylcholine. The occurrence of conduction block is not related to changes in longitudinal and transversal conduction velocity. Activation times increase as the coupling interval of the premature stimulus shortens, but are not different between acetylcholine and control experiments. Acetylcholine superfusion does not affect effective refractory period. The observations in these left atrial appendages from patients with AF suggest that acetylcholine induces conduction dispersion and unidirectional conduction block particularly after a short-coupled extra stimuli. Acetylcholine therefore influences the safety of conduction and facilitates the occurrence of reentry.
Proposed mechanisms of conduction modulation by the parasympathetic nervous system in the fibrotic human atrium

It is known that acetylcholine results in shortening of the action potential duration through activation of the inward rectifier K⁺ current I_{K\text{ach}}. Earlier animal studies have not found an effect on conduction of parasympathetic stimulation. However, in our human studies we observed a modulation of conduction of parasympathetic stimulation by high frequency stimulation of ganglion plexus in situ and acetylcholine superfusion in vitro. It is important to realize that the atria of the patients in our studies have a high amount of fibrosis. This differentiates these atria from atria found in most animal models. The presence of thick interstitial fibrotic septa alone might cause heterogeneity of conduction by propagation of the activation front around inexcitable barriers, especially with short-coupled premature stimuli. The additional electrophysiological changes induced by parasympathetic stimulation might facilitate conduction delay and block in this fibrotic substrate. The arrhythmogenic effects of acetylcholine on conduction, might be more noticeable in structurally remodeled atria than in normal healthy atria. We propose the following concepts on how the parasympathetic nervous system might influence conduction characteristics in our fibrotic human atria.

1) Direct electrophysiological effects: Acetylcholine activates the inward rectifier K⁺ current I_{K\text{ach}} which results in shortening of the action potential duration, but also in hyperpolarization of the resting membrane potential. The hyperpolarization reduces excitability of a cardiomyocyte as a larger amount of current is required to reach the activation threshold. Additionally, a rapid repolarization after phase 0 of the action potential due to stimulation of the inward K⁺ current via I_{K\text{ach}} results in a decreased plateau phase and decreased repolarization duration. The net potential gradient between cardiomyocytes is lowered and the safety of conduction is subsequently reduced.

2) Heterogeneity of parasympathetic effects: In our studies we observed an increased dispersion on conduction after parasympathetic stimulation. Heterogeneous effects on conduction facilitate unidirectional block. From anatomical studies have shown that an heterogeneous distribution of parasympathetic nerve fibers in the atrium. Similarly, parasympathetic stimulation results in a heterogeneous dispersion in refractoriness in the atrium. Alternatively, the density of I_{K\text{ach}} may show regional differences or there are regional differences in sensitivity to the effects of acetylcholine, which might result in a heterogeneous effect of parasympathetic stimulation.

3) Effect on intercellular coupling: Reduced phosphorylation has been observed after application of acetylcholine, which could change the function or expression of connexin 40 and 43 in the atrium. Decreasing intercellular coupling might be an indirect effect of acetylcholine that results in increased dispersion of conduction.
velocity and conduction block. However, little is known about the direct effects of acetylcholine on the more prevalent connexin 40 in the atrium. Further studies are required to test these hypotheses. However, it is important to note that these theories are not mutually exclusive and that a combined effect might be observed.

PART II: SURGICAL SUBSTRATE AND AUTONOMIC MODULATION FOR THE TREATMENT OF ATRIAL FIBRILLATION

Treatment of AF is a challenge for the cardiologist, despite increasing pharmacological and technological options. Although early studies of catheter ablation were promising, preventing the initiation of AF by isolation of the pulmonary veins has a moderate single procedure success rate of 57% to 77% with non-standardized follow-up protocols. This can be due to the fact that in most patients with recurrences the isolation lines are not complete. It is difficult to create a circular transmural ablation line with a small ablation catheter in a beating heart. Additionally, acute conduction block due to tissue edema might provide temporary conduction block during the procedure. Additional ablation lines can be created, that compartmentalize the atrium, to modulate the atrial substrate and prevent AF maintenance and macro-reentrant tachycardias. However, it is not clear whether these additional ablations lines increase the success rate of the ablation procedure and it is suggested that pulmonary vein isolation alone may be as effective as addition of additional ablation lines. Although pulmonary vein isolation and additional ablation lines may prevent the arrhythmia to initiate and perpetuate, they do not change the underlying pathophysiological mechanism. To influence underlying pathophysiological factors, autonomic modulation can be performed by ablation of the intrinsic cardiac nervous system as described in Chapter 2. The intrinsic cardiac nervous system is comprised of epicardial nerves that form the ganglion plexus, which are situated in the epicardial fatpads on the atrium. However, reaching and ablation of these ganglion fatpads with an endovascular approach can be challenging and there are no definite endpoints to assess successful ganglion plexus ablation.

Minimal invasive surgery for atrial fibrillation

Thoracoscopic pulmonary vein isolation is an invasive procedure. This minimal invasive surgical procedure tries to combine the success rate of surgical treatment with a less invasive intervention, consisting of three thoracoscopic surgical incisions instead of a sternotomy and cardiopulmonary bypass during conventional MAZE surgery. Potential advantages of the epicardial approach is a more thorough ablation scar due to the application of a bipolar ablation clamp and the possibility of ganglion plexus ablation. Finally,
the risk of embolic events might be reduced through the possibility of excluding the left atrial appendage during surgery.\textsuperscript{42}

In a systematic review, chapter 6, we analyze the first results of minimal invasive surgery in the treatment of AF. Twenty-three studies are included and they describe a single procedure success rate of 69% without anti-arrhythmic drugs and 79% with anti-arrhythmic drugs at one year follow-up. Due to the epicardial approach of minimal invasive surgery, there are other risks in comparison with catheter ablation. However, mortality is limited, especially compared to other cardiac operations, and appears to be similar to that of catheter ablation. However, surgical and post-procedural complications are frequently encountered. The risks of minimal invasive surgery are mainly comprised of peri-procedural problems. These complication rates can be explained through the procedural difficulty and the learning curve of the surgery. Altogether, these results show a promising role for minimal invasive surgery. Outcomes may benefit from standardization of the technique, results of longer follow-up and an improved patients selection. Similar to catheter ablation, the procedure is more effective in patients with paroxysmal AF. On basis of this review it is not possible to determine a reproducible and effective left atrial lesion and to assess the additional value of ganglion plexus ablation in minimal invasive surgery. However, electrophysiological measurements and confirmation of the ablation lines might be an important factor to increase the success of this procedure.

Electrophysiological guided thoracoscopic pulmonary vein isolation In the Academic Medical Center in Amsterdam a new hybrid approach to minimal invasive surgery was developed in 2008. This procedure is characterized by extensive periprocedural electrophysiological testing during thoracoscopic pulmonary vein antrum isolation and ganglion plexus ablation. In this approach cardiothoracic surgeon and electrophysiologist combine their expertise in the ablation of AF. In chapter 7 the first results of this procedure are described. Thirty-one patients are treated (16 paroxysmal AF, 15 persistent AF) in this study. Patients with non-paroxysmal AF are treated with additional left atrial ablation lines. Freedom of AF is assessed by electrocardiogram and Holter monitoring every 3 months or during symptoms of arrhythmia. Antiarrhythmic drugs are discontinued after 3 months. After 1 year, 19 of 22 patients (86%) has no recurrences of AF, atrial flutter, or atrial tachycardia lasting longer than 30 seconds and are not using antiarrhythmic drugs. Even with the small number of patients that we report in this study, these results make this technique a promising approach to the treatment of AF. In our view, the collaboration between surgeon and cardiologist is beneficial to the outcome of AF ablation. A minimal invasive surgical approach with thoracoscopic video-assisted surgery with pulmonary vein ablation and ganglion plexus ablation for AF is a safe and successful procedure. The electrophysiological guided thorough pulmonary vein isolation and ablation presumably contribute in achieving a high single procedure success rate.
In Chapter 8 we investigate the single procedure efficacy and safety of electrophysiological guidance, using two different groups with either an epicardial or endocardial electrophysiological guidance of thoracoscopic surgery for AF. In both approaches, an electrophysiologist contributes actively to the surgical procedure. Previously, a randomized multicenter study comparing catheter ablation and thoracoscopic surgery, showed superiority of the surgical approach (65.6% vs. 36.5% arrhythmia freedom at one year) in challenging patients with remodeled atria or prior failed ablation at the cost of an increase in adverse events. Our analysis is designed as an exploration of the value of electrophysiological guidance during two different electrophysiological guided thoracoscopic surgery approaches in these challenging patients with remodeled atria or prior failed catheter ablation. We demonstrate that electrophysiological guided surgical ablation for AF is effective in patients with enlarged left atria or a previously failed ablation. A total of 57 patients (79%) has freedom of AF and are off anti-arrhythmic drugs at one year follow-up (paroxysmal 83%, persistent AF 75%). Electrophysiological guidance of the procedure can be performed safely, either using an epicardial or using an endocardial approach, and may contribute to the success rate. Importantly, residual intraoperative conduction after surgical ablation and confirmation requiring additional ablation is detected with epicardial or endocardial mapping techniques in 50% and 11%, respectively. Additional epicardial or endocardial ablation is performed until bidirectional block was confirmed. A heart-team approach with close cooperation between surgeons and cardiologists resulting in an electrophysiological guided surgical ablation provides a new and promising treatment approach for these, often difficult to treat, patients.

**Future perspectives of minimal invasive treatment of atrial fibrillation**

Minimal invasive surgery of AF is a successful and safe treatment as shown in the studies in this thesis. It appears that electrophysiological guidance, either epicardially or endocardially, can increase the success rate of this procedure, without increasing peri-procedural complications. At this moment thoracoscopic pulmonary vein isolation is reserved to tertiary care centers. It is a complex procedure that requires close collaboration between electrophysiologist and cardiothoracic surgeon. In experienced centers thoracoscopic pulmonary vein isolation is a very effective alternative to catheter ablation of AF. Important for the future developments of minimal invasive surgery for AF is further standardization of the procedure in the different types of AF patients. Furthermore, the follow-up and definitions of success should comply with the latest guidelines to compare the efficacy and safety with established endovascular techniques.

The next step in the development of AF ablation, both for thoracoscopic and catheter ablation is proper patient selection and modifying the procedure based on individual patient and AF characteristics. AF is a multifactorial disease, but most ablation strategies are uniformly applied to all patients with a certain type of AF. Even though pulmonary
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vein isolation is effective, especially with an epicardial approach, the success percentage of pulmonary vein isolation is far from 100%. Other ablation strategies consist of ganglion plexus ablation, complex fractionated atrial electrogram ablation, ablation of linear ablation lines and rotor ablation.\textsuperscript{44,6,45} These additional ablation strategies with or without pulmonary vein isolation can be used to achieve an increased success rate. However, it is not clear which patient benefits the most form a certain ablation strategy. Further studies are required to identify the patients that benefit most from these specific ablation strategies or have severe AF that is not susceptible to invasive therapy. These studies should include imaging, biomarker and electrophysiological data to create a clinical classification of AF based on dominant pathophysiological mechanism.

The role of autonomic modulation in thoracoscopic pulmonary vein isolation for atrial fibrillation

In the Academic Medical Center in Amsterdam, targeted ablation of ganglion plexus has been performed during minimal invasive surgery.\textsuperscript{46} This form of autonomic modulation is common in minimal invasive surgery, although its role in epicardial surgery has never been thoroughly investigated. Otherwise, the ablation of ganglion plexus has been extensively studied in catheter ablation. Ablation of these ganglion plexus results in a reduced recurrence of AF in patient with paroxysmal AF.\textsuperscript{6} These studies show that anatomical ablation is currently the most effective method of localizing and subsequently ablation of these autonomic nerve structures.\textsuperscript{5} With epicardial surgery the epicardial fat pads in which these ganglion plexus reside, can be clearly visualized. However, it is not certain if additional ganglion plexus modulation during minimal invasive surgery is effective. Instead of a small ablation catheter used during endovascular pulmonary vein isolation, in thoracoscopic surgery a bipolar clamp is used.\textsuperscript{41} This clamp creates a large circular scar around the pulmonary veins. It is around these pulmonary veins the majority of the ganglion plexus and the majority of epicardial nerves are located.\textsuperscript{25} Therefore with ablation of the pulmonary veins a large proportion of the local autonomic nervous innervation may be ablated as well. Therefore, additional ganglion plexus ablation might not be necessary in epicardial ablation procedures. Withholding additional ablation of ganglion plexus might result in fewer ablation scars, that in the post-operative phase may facilitate atrial arrhythmias in particular atrial tachycardias. To answer some of these questions the AFACT trial has been performed at the Academic Medical Center (Atrial Fibrillation Ablation and Autonomic Modulation Via Thorascopic Surgery, clinicaltrials.gov NCT01091389). In this study, patients with paroxysmal or persistent AF were randomized to epicardial pulmonary vein isolation with or without ganglion plexus ablation. The results are expected in spring 2016. The outcome and the peri-procedural data of the AFACT trail will further help us understand the role of the autonomic nervous system, not only in minimal invasive surgery, but also in AF itself.
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REFERENCES


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