Clinical, electrophysiological and structural aspects of atrial remodeling

Lessons from thoracoscopic ablation of atrial fibrillation

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Chapter 1

General introduction and outline of the thesis

General introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in humans, affecting 2-4% of the population worldwide.[1] AF is characterized by an irregular heart rhythm, caused by unorganized electrical activation of the atria. Symptoms of AF may include palpitations, dyspnea, and fatigue, but in some patients, AF is asymptomatic, also known as silent AF. AF is associated with a three to fivefold increased risk of stroke, an increased risk of heart failure and death.[2, 3] Moreover, AF increases the risk of dementia and depression, and often comes with a decreased quality of life (QoL).[4, 5]

AF is an age-dependent disease, estimated to affect one in every three individuals aged 55 years and older.[6, 7] AF is often progressive, meaning that over time, episodes of the arrhythmia may occur more regularly, and the duration of episodes may increase (figure 1). We recognize five subtypes of AF, thought to represent different levels of disease progression.[3] The first symptomatic episode of AF is classified as 'new-onset AF'. This episode typically is of short duration and self-terminating. If AF occurs more often, and self-terminates within one week, that is classified as 'paroxysmal AF'. When symptomatic AF is terminated within one week with an electrical or chemical cardioversion, that is classified as 'paroxysmal AF' as well. With progression of the underlying substrate, AF may occur more often and its duration may increase, to the point where episodes do not self-terminate within one week. This is classified as 'persistent AF'. Further progression of AF may lead to continuous AF for longer than one year, classified as 'longstanding persistent AF'. AF may be accepted as rhythm if the symptoms are tolerable for the patient. Sinus rhythm is then no longer pursued. This is classified as 'permanent AF'. The above classification is practical for clinical use, but may not reflect the progression of the underlying atrial substrate.

There are two treatment strategies to manage symptomatic AF: rate control and rhythm control. A rate control strategy aims to prevent worsening of the ventricular function due to prolonged high and/or irregular heart rate (tachycardiomyopathy), by reducing the heart rate. If a rate control strategy does not provide sufficient symptom relief, a rhythm control strategy is preferred. A rhythm control strategy aims to restore and maintain sinus rhythm. In this thesis, we focus on patients in whom a rhythm control strategy is pursued.

The mechanisms of AF

Three key ingredients are required for the genesis AF: a trigger to initiate AF, a substrate to sustain AF, and modulating factors. These ingredients are better known as the Triangle of Coumel.[8] The trigger of AF is focal activity; abnormal activation of one or several myocardial cells, able to provoke the arrhythmia. In 1998, the pulmonary veins were described as the main source of high frequency triggers.[9] Focal activity, usually triggered activity (i.e. early or delayed afterdepolarizations) can be due to disturbances of the membrane potential of a single cell, leading to spontaneous depolarization. Altered automaticity can also lead to spontaneous depolarization of myocardial tissue. While micro re-entry, re-entry in only a few myocardial cells, is mechanistically different from focal, triggered activity, it is considered focal activity, as conventional electrophysiological mapping techniques are unable to distinguish micro re-entry from true focal activity.

Focal activity can create a pro-arrhythmogenic environment, but needs re-entry to result in AF. Re-entry can be subdivided into anatomical and functional re-entry. Anatomical re-entry occurs when the atrial activation front travels in a circuit, around an anatomical obstacle that is unexcitable. The activation front activates previously excited tissue like a snake chasing its tail. Reentry can only exist when the total activation time of said circuit is longer than the repolarization time of the tissue. Reduced conduction velocity and/or shortening of the action potential duration, and thereby refractoriness, support the possibility of reentry and thus AF. Functional re-entry occurs in the same way around a functional zone of conduction block, but without an anatomical obstacle.

Functional re-entry is the main component of the three main mechanisms of AF. The leading circle concept describes a re-entry phenomenon without an anatomical obstacle.[10] The center of the re-entry wave is invaded by multiple wavelets, shows electrotonic depolarizations that prevent it from regaining full excitability, and therefore left unexcitable by the circulating wave. The rotor activity theory describes spiral wave activity around an excitable but not excited center, with a typical curved wavefront.[11] The multiple wavelet theory suggest perpetuation of AF by random propagation of multiple simultaneous re-entry circuits throughout the atria. AF would be sustained while the number of wavelets exceeds a critical level.[12]

AF substrate

The atrial arrhythmogenic substrate is the result of atrial remodeling; complex pathophysiologic changes of the tissue due to various stressors, including ageing, other cardiac disease, and atrial fibrillation itself. Figure 2 schematically displays the principal AF promoting mechanisms in red boxes. Signs of atrial remodeling develop long before the first onset of AF.[13] Electrical remodeling includes all changes of the electrical function of the atria that enable atrial fibrillation. Shortening of the action potential duration and slowing of the atrial activation front increase the chance of reentry. Abnormal calcium handling and autonomic activation or dysfunction promote AF-initiating triggers. There are multiple positive feedback loops promoting atrial remodeling during AF, increasing the stability of AF and thereby the risk of AF recurrence (Figure 2).

After initiation of AF, the increased activation frequency causes myocardial cells to load with Ca^{2+}. Reactive mechanisms downregulate I_{CaL} to reduce calcium influx and increase inward K^+ rectifier (I_{K1})[14], which decrease the action potential duration and refractory period, contributing to the pro-arrhythmogenic environment. Furthermore, I_{k1} and I_{KACh} are increased, both contributing to action potential duration shortening.[15] Furthermore, impaired calcium handling may lead to contractile dysfunction and contributes to tachycardiomyopathy.[16]
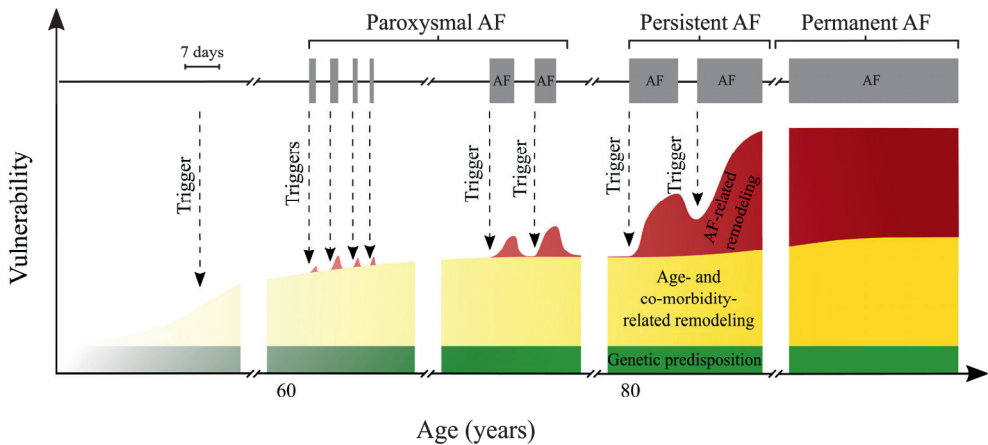
Figure 1. A framework of AF initiation, maintenance and progression, based on Heijman et al. Circ. Res. 2014[26]. AF onset is dependent on substrate vulnerability and triggers, as described by Heijman et al [26]. Within the present study vulnerability and triggers are combined in to a single factor—activation rate. Activation rate is then dependent on a constant genetic predisposition, time-varying age/co-morbidity-related remodeling, AF-induced remodeling dependent on AF history and trigger events. Physiological changes may increase both the rate of a trigger event occurring and likelihood of AF episode initiation following a trigger event. Over time, some patients progress on to paroxysmal, persistent and permanent AF as their substrate vulnerability and frequency of trigger events increases. Note the timescale for AF triggers and episodes is distinct from the lower axis and is expanded for clarity. Source: Chang ETY, Lin YT, Galla T, Clayton RH, Eatock J (2016) A Stochastic Individual-Based Model of the Progression of Atrial Fibrillation in Individuals and Populations. PLoS ONE 11(4): e0152349. https://doi.org/10.1371/journal.pone.0152349 [27]

Structural remodeling

Structural remodeling refers to a variety of changes of the atrial myocardium, resulting in atrial dilatation, inflammation, cellular hypertrophy, fibroblast proliferation and deposition of extracellular matrix proteins in the extracellular space.[17] Extracellular matrix deposits consist of collagens, glycoproteins and proteoglycans, and its excessive deposition is generally referred to as atrial fibrosis. Fibrotic depositions in the myocardium can interfere with the atrial conduction pattern. Propagation of the activation front may be slowed due to zigzagging myocardial pathways and decreased conduction velocity as described in infarcted papillary muscle bundles.[18] Fibrosis may increase anisotropy, which may lead to paradoxal increase of longitudinal conduction velocity along myocardial bundles.[19, 20] Hence, structural alterations of the myocardium through myocardial fibrosis may facilitate longer pathways of activation, conduction block and thereby facilitate reentrant activation. Lastly, fibroblasts and myofibroblasts are able to electrically couple with cardiomyocytes through gap-junctions, which decreases conduction velocity and maximal depolarization level.[21] Of note, this mechanism has been demonstrated in cell cultures but not in intact hearts. Consequent depolarization-induced automaticity may result in ectopic activity[22] and further increase the vulnerability for persistent AF.

Complexity of the atrial activation during AF

During the course of the arrhythmia, progression of electrical and structural remodeling coincide with clinical progression from paroxysmal AF to persistent forms, with an increasingly complex pattern of activation during AF. During sinus rhythm, the atria are activated in a planar and organized fashion with one activation wave at a time. During AF, simultaneous multiple wavelets activate throughout the atria. Consequent shortening of the action potential duration and slowing of the activation propagation create an environment favorable for AF maintenance. This phenomenon where ongoing AF facilitates its perpetuation is commonly referred to as 'AF begets AF'.[23]

Atrial fibrillation waves continuously initiate, break up, die down, and traverse from epi- to endocardium or vice versa. The number of fibrillation waves and endo-epicardial breakthroughs are thought to reflect the severity of atrial remodeling.[24, 25] Reconstruction of fibrillation waves requires simultaneous recording of multiple electrodes, and is not possible with single electrode endocardial catheters. After reconstruction of the activation pattern, the complexity of AF can be expressed as the number of simultaneous fibrillation waves, ratio of local- to nonlocal activations (fractionation index), and the dissociation of endo-epicardial activation evidenced by breakthrough waves.[24, 25]
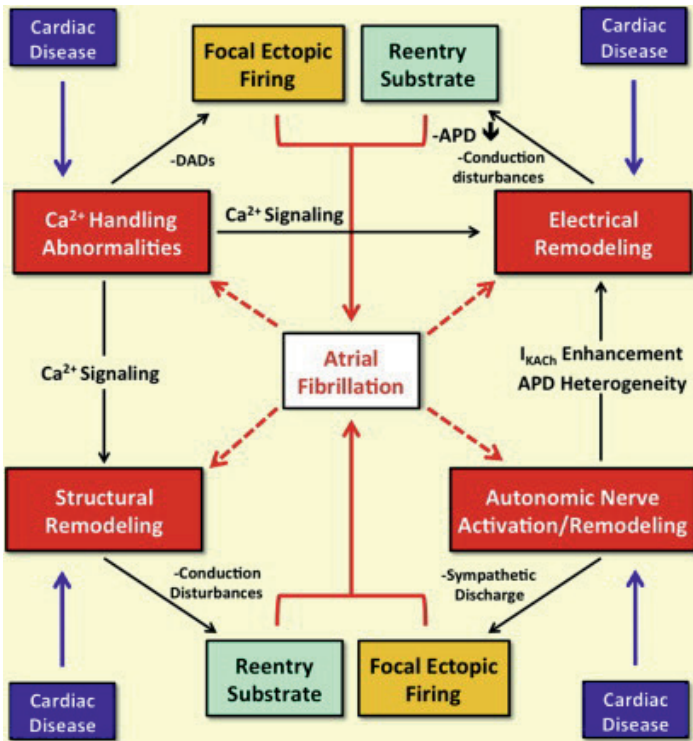
Figure 2. The principal AF-promoting mechanisms resulting from AF-inducing remodeling are shown in red boxes. Focal ectopic firing is usually due to DADs that reach threshold and cause spontaneous AP generation. A susceptible reentry substrate requires abbreviated refractoriness (which depends primarily on APD) and/or conduction abnormalities. These mechanisms can be the result of AF-promoting cardiac diseases but can also result from the consequences of AF itself. AF = atrial fibrillation; APD = action potential duration; DADs = delayed afterdepolarizations; IKACh = acetylcholine-regulated K+ current. Reprinted from Journal of the American College of Cardiology, Vol. 63, 22 (2014) Nattel & Harada, Atrial Remodeling and Atrial Fibrillation: Recent Advances and Translational Perspectives [28], with permission from Elsevier.

Therapeutic approaches for AF

Stroke prevention

Treatment of AF consist three main pillars: Stroke prevention, cardiovascular risk reduction, and symptom management. The risk of stroke can be effectively reduced with the use of oral anticoagulants.[29] Novel oral anticoagulants (NOAC) or vitamin K-antagonist are mostly used for anticoagulation, depending on patient characteristics, medical history and risk of bleeding. With the CHA_2DS_2VASc and HASBLED scores, the yearly risk of stroke versus bleeding can be assessed.[30] According to the current guidelines, oral anticoagulation in patients with documented AF should be considered with a CHA_2DS_2VASc score of 1, and is recommended from a score of 2.[3]

Cardiovascular risk reduction

To improve the general health, and improve efficacy of therapy for AF, other reversible cardiovascular risk factors should be adequately treated. These risk factors include hypertension, heart failure, coronary artery disease, obesity, sleep apnea and thyroid disease. Optimization of risk factors may improve symptoms of AF, and reduce the risk of recurrent AF.[31] Of note, in the presence of multiple risk factors, treatment of one individual risk factor may not be enough. [32] Untreated risk factors may mitigate the effect of rhythm control therapy. Importantly, and apart from the effect that controlling cardiovascular risk factors may have on efficacy of rhythm control therapy, these risk factors in itself may individually affect the progression of atrial remodeling and the atrial fibrotic substrate.

The risk of cardiovascular disease has, at least in the laymen literature, long been associated with an unhealthy lifestyle. Obesity, alcohol use and lack of exercise are generally bad for the heart. Recently, researchers have demonstrated improved maintenance of sinus rhythm in patients with AF and heart failure who were subjected to targeted therapy including physical activity, dietary restrictions and counselling.[33] Weight loss is beneficial for patients with AF, and may even reverse AF progression. In the LEGACY trial, patients with ≥10% weight loss and optimal risk factor management maintained sinus rhythm in 45% of those patients, without the need for antiarrhythmic drugs or ablation.[34] Moderate exercise and physical activity have positive effects for cardiovascular health and may help reduce the risk of AF.[35] However, prolonged and vigorous physical activity can increase the risk of atrial fibrillation; elite and endurance athletes (marathon, triathlon etc.) have a 2.5-fold higher incidence of atrial fibrillation compared to subjects who do not perform endurance sports.[36] There seems to be a U-shaped curve where both a lethargic lifestyle and long-term vigorous activity are associated with increased risk of AF.[35]

Symptom management

Symptomatic AF can be treated in one of two strategies: by reducing the ventricular rate during AF(rate control strategy), or by preventing the arrhythmia (rhythm control strategy). Rhythm control is preferred in patients with symptomatic AF despite adequate rate control.[3] Acute rhythm control can be effectively achieved with electrical or pharmacological cardioversion.[37] Successful cardioversion restores sinus rhythm and

thereby reduces symptoms of AF, but does not affect or treat the underlying disease leading to AF (among which the arrhythmogenic substrate).

Antiarrhythmic drugs

Antiarrhythmic drugs (AAD) can be used in both rate and rhythm control strategies. The effect of AAD on the action potential is categorized with the Vaughan Williams classification. Class II, IV and V AAD are recommended for rate control, while class I and III are recommended for rhythm control therapy.[3] In this thesis, the term AAD is used for class I and III antiarrhythmics. AAD therapy does not offer a survival benefit compared to a rate control strategy.[38, 39] The EAST-AFNET4 trial demonstrated benefit of early rhythm over usual care on a composite endpoint of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome.[40] A sub-analysis demonstrated that early rhythm control is mainly beneficial for patients with many comorbidities (CHA$_2$DS$_2$VASc score of ≥4).[41] Unfortunately, adverse effects of AAD's, such as bradycardia, drug toxicity, hypotension and ventricular arrhythmia are common, and may not be tolerable for some patients. If AAD therapy fails to provide adequate symptom reduction, invasive therapy may be considered.

History of invasive therapy

The first invasive therapies for AF include the sinus node – atrioventricular isolation 'corridor' operation and the surgical Cox-maze procedure.[42, 43] The Cox-maze procedure included a multitude of surgical incisions and sutures in the left and right atrium, which developed into nonconductive scar tissue (figure 3). Fortunately, this included isolation of the pulmonary veins, as the recognition of the PV's as important triggers for AF was ten years later.[9] The Cox-maze III procedure reported 95% freedom of AF after 5 years follow-up, and became the gold standard for surgical ablation of AF.[44, 45] However, follow-up was based on telephonic interviews, ECG's were sparse and holter monitoring was not performed. Recurrence of AF and repeat procedures were not reported. The surgical Cox-maze procedure was a highly complex and technically difficult procedure with a considerable risk for pacemaker implantation or death.[45] The complexity of the procedure may have contributed to its limited application. The Cox-Maze procedure remained a niche until catheter ablation was introduced. Technological innovations enabled the implementation of thoracoscopic techniques, radiofrequency and cryoablation in the Cox-maze IV procedure, making the procedure technically easier. By omitting the need for incisions in the heart, the procedure could be performed on a beating heart, reducing complications and the total procedure time. This made the less invasive Cox-maze IV procedure an effective and safe procedure.[46]
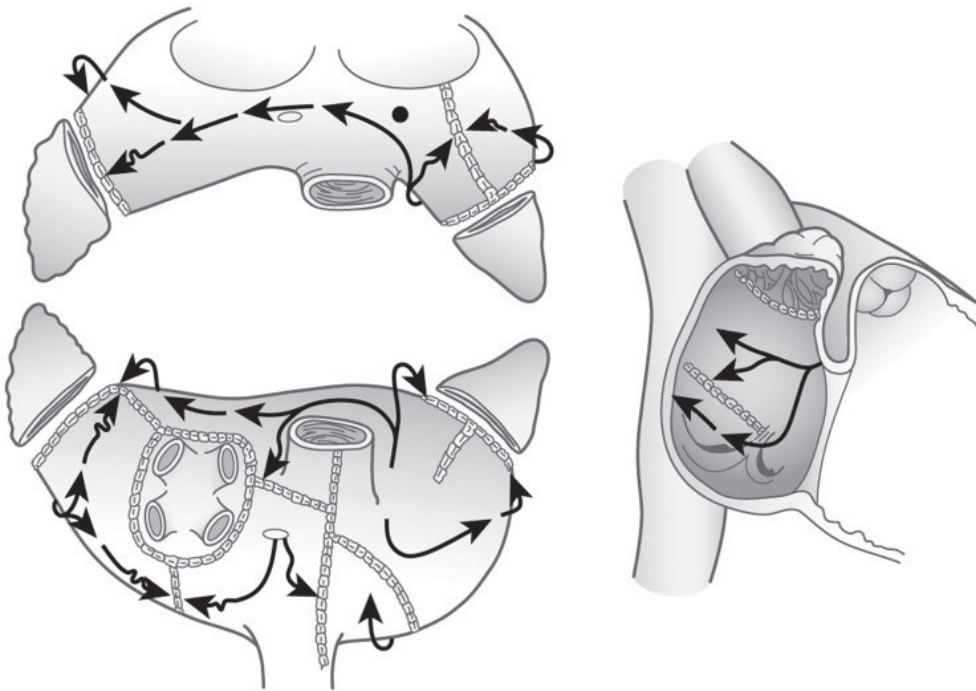
Figure 3. The original 'cut-and-sew' (Cox-maze III) procedure. Reproduced from Ruangsri et al. The Cox-maze IV procedure in its second decade: still the gold standard? Eur J Cardiothorac Surg. 2018 Apr 1;53(suppl_1) i19-i25, by permission of Oxford University Press.

Catheter ablation

The identification of the pulmonary veins as the main triggers of AF revealed the importance of pulmonary vein isolation in the treatment of AF.[9] Up to today, pulmonary vein isolation remains the cornerstone of AF ablation and is therefore recommended as an endpoint in all AF ablations.[47] Radiofrequency catheter ablation is currently the mostly used technique to perform pulmonary vein isolation. A long, thin catheter of mere millimeters is brought up to the heart through a punction in the groin. After passing the inter-atrial septum to get into the left atrium, the tip of the catheter is maneuvered against the endocardium. Then, an alternating current of 100-2000 kHz is applied between the tip of the electrode and a large remote body surface electrode. This current evokes resistive heating of the tissue directly under the electrode, reaching temperatures over 50 degrees Celsius. This causes denaturation of proteins and consequent tissue necrosis. Over time these damaged cells develop to a nonconductive scar. The challenge of catheter ablation resides in applying enough energy to create a transmural and continuous lesion, without damaging underlying tissue, such as the esophagus or phrenic nerve. Modern catheters not only deliver radiofrequency energy, but can simultaneously record endocardial electrograms, the force applied at the tip of the catheter, the tip temperature and tissue impedance. Room-temperature saline is ejected through tiny holes in the tip of the catheter to prevent clotting

and charring by excessive heating of the tissue. These technologies help the cardiologist to improve the lesion quality and reduce risk of complications. Pulmonary vein isolation (PVI) can be achieved by repeatedly applying energy point-by-point in a wide circle around the pulmonary vein antrum.

There is general consensus that PVI alone is sufficient to effectively treat paroxysmal AF.[47] However, high recurrence rates after PVI in patients with persistent and long-standing persistent AF resulted in identification of several additional ablation targets. Unfortunately, initially promising results did not lead to structural improvement of recurrent AF. Recently the STAR AF II trial demonstrated that additional ablation beyond PVI in patients with persistent AF does not improve freedom of AF.

Catheter ablation is superior to antiarrhythmic drugs on AF recurrence and quality of life in multiple studies.[48-51] Catheter ablation is therefore recognized as an effective treatment in patients with paroxysmal AF.[3] However, in patients with persistent or long-standing persistent AF, the efficacy of catheter ablation remains suboptimal. One year freedom of AF is about 50% [52], leading to redo procedures.

Thoracoscopic ablation

The acclaimed high success rates of the Cox-maze procedure fueled the development of a less invasive surgical alternative. Particularly for patients who are less suitable for catheter ablation. This resulted in a video-assisted totally epicardial bilateral pulmonary vein isolation.[53] The first published results of these procedures were promising, with 70% freedom of atrial arrhythmia after one year.[54] Due to a relatively high number of atrial tachycardia's as recurrence, hybrid approaches were designed.[55] This initiated a close collaboration between surgeon and electrophysiologist, with confirmation of conduction block and additional ablation in case of persistent conduction.[56, 57] A comparison between endocardial and epicardial confirmation of conduction block revealed no difference in outcome.[58]

The technical advantage of epicardial ablation during thoracoscopic surgery over endocardial catheter ablation is the use of an ablation clamp to electrically isolate the pulmonary veins. The pulmonary vein antrum is placed in between the jaws of the clamp, and closing of the clamp fixates the tissue and focusses bidirectional RF energy between the two jaws. This abolishes the heat sink effect of circulating blood, and creates a continuous transmural ablation line. Furthermore, during thoracoscopic (and open) surgery the left atrial appendage can be removed, which reduces the risk of ischemic stroke or systemic embolism.[59]

The first randomized trial comparing catheter ablation and thoracoscopic ablation demonstrated superiority of thoracoscopic ablation, at the cost of more procedural complications.[60] Later randomized and non-randomized studies demonstrated the same trend[52] while increasing experience with thoracoscopic ablation may reduce the risk of complications.[61] Initially thoracoscopic ablation was mainly used as a last resort for patients in whom catheter ablation was deemed futile. Thoracoscopic ablation has shown to be an effective treatment for patients with enlarged left atria, previously failed catheter ablation(s) and persistent and longstanding-persistent AF.[60] The optimal invasive treatment and strategy of persistent AF has not yet been established. This is in part because

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our understanding of the arrhythmogenic substrate in persistent AF is incomplete. Current guidelines state thoracoscopic ablation may be considered in patients with drug-refractory AF and prior failed catheter ablation, or with evident risk factors for catheter ablation failure, or if the patient prefers thoracoscopic treatment.[3] Nowadays, thoracoscopic AF ablation is a widespread and accepted treatment for AF, while remaining a niche compared to catheter ablation.

Outcome

The goal of AF ablation is to relieve AF-related symptoms and to improve the quality of life, which can be achieved through successful elimination or reduction of the burden of AF.[62] The HRS/EHRA/ECAS/APHRS/SOLEACE expert consensus statement recommends the use of the following definition of AF recurrence: freedom from any atrial arrhythmia >30s off antiarrhythmic therapy. During a three month blanking period right after the procedure, recurrences are not considered a failure of the procedure. In the meantime, the clinical relevance of this definition and the optimal outcome measure remain under debate.[63]

Risk factors for AF recurrence after ablation

Before patients undergo ablation for atrial fibrillation, patients are systematically screening for risk factors for AF recurrence. Optimization of modifiable risk factors may improve the chances of freedom of AF after the procedure. Modifiable risk factors include sleep apnea, hypertension, hyperlipidemia, diabetes mellitus and heart failure.[3] Obese patients may benefit from significant and sustained body weight reduction; ≥10% sustained weight reduction may improve AF related symptoms similar to a catheter ablation, without the risk of procedural complications.[64] Furthermore, reduction or cessation of alcohol intake and smoking may improve the efficacy of AF therapy.

Non-modifiable risk factors include (but are not limited to) patient age, persistent or longstanding persistent AF, enlarged left atrium, duration of AF, reduced left ventricular ejection fraction and renal dysfunction. [65, 66] Multiple studies reported that females are at higher risk of recurrent AF.[67] On top of that, women have a higher risk of procedure related complications[68, 69], which is possibly due to smaller anatomy of the heart. It remains unclear if a failed catheter ablation in itself is a risk factor for recurrent AF.[70, 71] One possible explanation is that patients with a failed catheter ablation have more clinical risk factors for recurrent AF. A comparison between patients with and without previously failed catheter ablation and their clinical outcome could demonstrate if these patients are at greater risk of recurrence due to worse clinical characteristics.

Outline of this thesis

Part one of this thesis focusses on clinical risk factors for the recurrence of AF. Chapter 2 describes the differences between women and men undergoing thoracoscopic AF ablation and their respective risk factors for recurrence. In a subgroup of patients, we analyzed the proportion of epicardial and endocardial collagen between women and men. In Chapter 3 we assessed the effect of giant left atrium on the freedom of AF after thoracoscopic ablation. Chapter 4 presents the results of an international multicenter trial investigating whether a previously failed catheter ablation is a marker of reduced efficacy of thoracoscopic AF ablation. In this study we performed propensity score matching to compare these patient groups as unbiased as possible.

Part two of this thesis focuses on the electrical and structural atrial substrate as a marker for prognosis after thoracoscopic ablation. In Chapter 5 we analyzed the relation between left atrial epicardial conduction time (LAECT) and two-year recurrence of AF. First, the right pulmonary veins were isolated, a partial roofline was constructed connected to the trigone line. We measured LAECT as the time to local activation at one side of the roofline upon pacing from the other side and analyzed collagen fibre density in histologic sections of the left atrial appendage. In Chapter 6 we performed high density epicardial mapping of AF and assessed the complexity of the atrial activation pattern. We determined local activation from the unipolar electrograms and reconstructed the atrial fibrillation wavefronts. From these data we assessed the complexity of AF.

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