Clinical, electrophysiological and structural aspects of atrial remodeling

Lessons from thoracoscopic ablation of atrial fibrillation

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Publication date
2023

Chapter 7

General discussion & future perspectives

Atrial fibrillation is a complex, multifactorial, and progressive disease. Despite vast amounts of research, mechanisms of AF and AF progression remain incompletely understood. With increasing life expectancy and general ageing of the population, the burden of AF on healthcare and healthcare budgets increases.[1] Prevention and effective treatment of AF are needed to manage the expected increase in AF-related healthcare. However, effective primary and secondary prevention of AF are still lacking. For effective primary prevention, specific identification of subjects at high risk for AF is necessary. However, due to the complexity of AF, and the incomplete understanding of AF mechanisms, current prediction models for AF remain suboptimal.[2] Moreover, treatment of AF (secondary prevention) remains incompletely effective. Thus, the mechanisms of AF should be further explored and patient-, physiological- and pathophysiological characteristics defined.

This thesis presents clinical, electrophysiological and tissue characteristics associated with recurrent AF after thoracoscopic ablation. All studies encompass the analysis of patients from a well-documented cohort of patients, undergoing a structured preoperative investigations and follow-up regime.[3-5] This enabled a fair comparison between (subsets of) patients and their clinical outcome after the procedure. We investigated patients undergoing thoracoscopic AF ablation, originating from the cut-and-sew Cox-maze procedure. The original Cox-maze procedure was a complex open chest surgical procedure, involving a multitude of incisions in the left and right atrium, with the need for extracorporeal circulation. The procedure was improved twice, to reduce the need for pacemaker implantations, reduce arrhythmia recurrence and improve long-term atrial function.[6, 7] The third iteration of the Cox maze procedure (Cox-Maze III) became the gold standard for surgical treatment of AF in the 2007 guidelines.[8] The last and current version, the Cox-maze IV uses cryothermal- or radiofrequency ablation, omitting the need for incisions in the heart and thereby reducing the complexity and complication risk of the procedure.[9] Moreover, an adapted version can be performed totally thoracoscopically.[10] Despite the higher efficacy of thoracoscopic AF ablation compared to catheter ablation, thoracoscopic AF ablation remains a niche market compared to catheter ablation.[11] This may partly be due to the lack of randomized trials comparing the efficacy with catheter ablation, the relative invasiveness, the lack of standardization of the procedure and the selection of patients for stand-alone thoracoscopic ablation.

The majority of patients included in this thesis were treated in the Amsterdam UMC, a tertiary care center in The Netherlands. Patients underwent an elaborate screening process prior to the procedure and are thus a selected population with (severely) symptomatic AF. Patients selected for thoracoscopic ablation generally have advanced symptomatic AF, which is often persistent, have enlarged left atrium or a previously failed catheter ablation.[3, 5] The procedures were performed by experienced cardiothoracic surgeons, guided by an electrophysiologist to confirm conduction block, or aid the surgeon into additional ablation at specific locations.[4, 12]

Sex differences

Differences between females and males in clinical presentation, epidemiology and pathophysiology may affect the effectiveness of AF treatment. Unfortunately, women are generally underrepresented in randomized clinical trials, which may have contributed to a lack of sex-specific diagnostic and therapeutic guidelines, except those on the prevention

of thrombo-embolic events.[1] Therefore, we investigated sex-specific characteristics of patients undergoing thoracoscopic AF ablation in **chapter 2**. We compared females and males undergoing thoracoscopic AF ablation with regard to clinical presentation, outcome and atrial fibrosis.

In our study, women were older, but had fewer cardiovascular risk factors, less myocardial infarctions and less vascular disease. After two years follow-up, females had more recurrence of AF, and female sex was independently associated with increased recurrence of AF. These findings are in line with other contemporary studies.[13] We demonstrated that women without a certain risk factor for recurrence, for example left atrial enlargement, have similar outcome as men with that risk factor, suggesting that female sex in itself is an important factor contributing to the outcome of AF treatment. These data underscore the lack of mechanistic sex-specific understanding of AF and AF recurrence. However, there are indications that the pathophysiological changes in the atrial myocardium that underlie the substrate of AF in females are not similar to males.[14] A recent observational study analyzed sex differences in patients undergoing repeat catheter ablation for persistent AF. This study showed that females tended to present with organized arrhythmia recurrence (atrial tachycardia or atrial flutter) more often than males. Moreover, one third of the females had no reconnected PV's at repeat catheter ablation, compared to 20% in males, which suggests substrate based recurrence plays a more important role than trigger based (due to reconnected PV's) recurrence in females.[15] Indeed, females may demonstrate more atrial fibrosis on late enhancement MRI compared to males.[16] In our histologic analysis of left atrial appendage tissue, we found more endo- and epicardial fibrosis in females compared to males. It seems contradictive that women have more atrial fibrosis, while the arrhythmia presents itself later in life.[17-19] This may imply that women can endure more substrate progression compared to men before the arrhythmia occurs, or that women are somehow protected for the arrhythmia for a longer time. One study reported a reduced shortening of the effective refractory period in pre-menopausal women compared to post-menopausal women, suggesting that estrogen mediates a protective effect on AF.[20] In our study, most women were of post-menopausal age, and data on hormone replacement therapy were unavailable.

Females experience decreased efficacy of rhythm control therapy compared to males, and the underlying mechanisms remain understudied and thereby largely unknown, leading to underperformance of females undergoing rhythm control therapy. This observation, however, carries the promise of a greater potential for improvement of rhythm control therapy if we succeed in developing sex-specific diagnostic and therapeutic strategies. Factors necessary to succeed in sex-specific strategies are 1) understanding the key differences between women and men, 2) assessing whether women in clinical practice should qualify for ablation or for alternative treatments, 3) systematic follow-up of procedures, particularly in standard clinical care, and 4) patient reported outcome data. Sex-tailored treatment strategies can be the first step towards individualized AF treatment

Giant left atrium

Thoracoscopic ablation is a considered a robust alternative to catheter ablation for patients with advanced AF, with improved freedom of AF at the cost of more procedural complications.[11] In patients in whom the efficacy of catheter ablation is reduced (patients with persistent AF, enlarged left atrium and other risk factors for recurrence), thoracoscopic AF ablation may be an appropriate alternative. Indeed, in patients with persistent AF thoracoscopic ablation was associated with a mere 20% lower rate of AF recurrences than catheter PVI.[11] However, contrary to catheter ablation, where an enlarged left atrium is associated with more AF recurrences after ablation [24], the success of thoracoscopic AF ablation in patients with extremely enlarged left atrium remained unknown. We investigated the outcome of patients undergoing thoracoscopic AF ablation with severely enlarged left atrium in **chapter 3**. In patients with giant left atrium (LAVI ≥ 50 ml /m2), one year freedom of AF was 55%, and two year freedom of AF was 43%.[25] While these percentages may appear poor, previous studies demonstrated that 90% of patients with AF recurrence have a maximum of three documented recurrences per year.[26] Moreover, 85% of patients report an improvement of quality of life.[27] Patients with a giant left atrium had equally few adverse events as patients without a giant left atrium. As these patients are not suitable for catheter ablation due to low expected success rate, thoracoscopic ablation is a safe and effective option.

Failed catheter ablation

To the best of our knowledge, the first association between a previously failed catheter ablation with increased risk of AF recurrence after thoracoscopic ablation was suggested in 2017.[21] In **chapter 5** of this thesis, we investigated the role of a previous ablation with regard to patient characteristics and outcome of the thoracoscopic procedure in a cohort of patients with persistent AF and 2 years follow-up. Patients with a previously failed catheter ablation had more AF recurrence. Following, we hypothesized that these patients have a higher risk of recurrent AF. In **chapter 4,** we compared patients undergoing thoracoscopic ablation with and without a previously failed catheter ablation in a large retrospective multicenter study. We found that patients with a previously failed catheter ablation indeed have higher risk of recurrence, but that these patients do not have more risk factors for recurrence. If any, these patients had fewer risk factors for recurrent AF. This finding is in line with previously published studies.[21, 22] The study of Lim et al. demonstrated no difference in outcome, while patients with a failed catheter ablation were younger, had more paroxysmal AF and smaller LAVI.[23] With these characteristics, patients with a failed catheter ablation may be expected to experience improved chances of AF freedom.

Our study merely identifies an increased risk of recurrence in these subjects, and per study design, we cannot comment on causality. Thus, we identified a failed catheter ablation as a marker for reduced efficacy of thoracoscopic ablation. Since a causality study is impossible, one of the next steps is to assess the optimal strategy for AF ablation. There is consensus that catheter ablation with pulmonary vein isolation is sufficient therapy in patients with paroxysmal AF.[1] However, for patients with persistent AF it remains unclear whether catheter or thoracoscopic ablation should be performed first. Moreover, the optimal lesion set remains unknown, and after the sobering landmark trial STAR AF II, PVI alone appears sufficient during the initial procedure. However, and irrespective of the findings in STAR AF

II, as outlined above, a previously failed catheter ablation represents a risk for procedural failure of thoracoscopic AF ablation. Therefore, the ongoing APPROACH AF study investigates whether catheter or thoracoscopic ablation, confined to PVI only, is the optimal first choice for patients with persistent AF (NCT04715425). This landmark trial will guide cardiologists in choosing the optimal treatment strategy.

Electrophysiologic markers

Aside from anatomical considerations outlined above and in **chapter 3**, we further investigated physiological mechanisms and markers associated with reduced efficacy of AF ablation. In **chapters 5 and 6**, we identified several electrophysiological markers and compared these with baseline patient characteristics and the outcome after the procedure. Longer left atrial epicardial conduction time was associated with more AF recurrence.[22] Furthermore, increased fibrosis fiber density was associated with shorter left atrial epicardial conduction time. This seemingly counterintuitive finding may result from more anisotropy: more preferential conduction along fibrosis fibers.[28] Activation time is the product of conduction velocity and distance traveled of the atrial activation front. In our study, left atrial size and volume did not correlate with the activation time, which may suggest that conduction velocity is an important determinant of activation time, and thus reflects the pathophysiological structural and electrical remodeling of the atrial myocardium. Decreased atrial conduction velocity has been associated with AF, but its relation to the atrial substrate so far remains unknown.[29, 30] Atrial fibrosis may result in zig-zag activation, altering the activation pathway, as demonstrated in infarcted papillary muscle.[31] Moreover, electrical coupling of fibroblasts to myocardial cells may reduce conduction velocity at a cellular level[28, 32, 33] Detailed assessment of conduction velocity may thus provide a reflection of atrial remodeling processes beyond electrical remodeling alone, but for pragmatic reasons we restricted our analysis to conduction times.

In **Chapter 6,** we assessed characteristics and activation patterns of atrial fibrillation. We described patients in three conceptual groups of increasing clinical complexity of AF: patients with paroxysmal AF, patients with persistent AF in sinus rhythm at the start of the procedure and patients with persistent AF with ongoing AF. Along these groups, the AF cycle length and fractionation index gradually increased, suggesting increasing levels of electrical and structural remodeling. A higher left atrial fractionation index was associated with more interstitial fibrosis in histological sections of the left atrial appendage of the same patients. Moreover, the difference in AF cycle length between left and right atrium was associated with freedom of AF during follow-up. Finally, electrophysiological left atrial properties (voltage, slowing of conduction) may not improve after successful ablation in terms.[34] Therefore, the quantification of electrical or structural remodeling may provide a robust reflection of progression of AF and prognosis of therapy.

Fibrosis

Atrial fibrosis is defined as proliferation of myocardial fibroblasts, differentiation into alpha-smooth muscle actin (α-SMA) expressing myofibroblasts and the accumulation of extracellular matrix (ECM) proteins and contributes to the structural myocardial changes that form the substrate of atrial fibrillation. Fibrosis is induced through various stressors, including age, cardiovascular morbidities, and the heart rhythm itself. Complex molecular and neurohumoral pathways cause atrial fibroblasts to activate, proliferate, and

differentiate, thereby producing extracellular matrix proteins. Extracellular matrix proteins form a crucial part of the structural integrity of myocardium, but excessive extracellular matrix deposition is thought to affect activation characteristics responsible for atrial fibrillation. However, there is no histologic evidence on the relation between burden of cardiovascular disease and atrial fibrosis in patients with AF.[35] Magnetic resonance imaging (MRI) studies such as DECAAF demonstrate an association between increased MRI detected late gadolinium enhancement (a measure for fibrosis) and more AF recurrence after catheter ablation.[36] Unfortunately, the reproducibility of these methods remains questionable and MRI assessment of the fibrotic atrial substrate is not being widely applied in clinical care. Moreover, the clinical implication is limited, as subsequent ablation of MRI-identified fibrotic areas as a strategy to reduce their pro-arrhythmogenic properties, did not improve outcome of the procedure.[37] Therefore, the documentation of atrial fibrosis is currently only a marker for clinical outcome. Evidence of fibrosis affecting electrical conduction patterns or voltage distribution is sparse, partly due to the difficulty of combined assessment of electrical and histological characteristics in the same human tissue sample. Interstitial and endomysial fibrosis may alter conduction patterns contributing to AF.[28, 38] However, a recent study demonstrated lack of association between (right atrial) fibrosis and conduction abnormalities and low voltage areas.[39] **Chapter 6** confirms the complex relation between fibrosis and electrophysiological characteristics of the left atrium. These studies underline that fibrosis is not the only culprit for AF and the complex mechanisms and interplay of fibrosis, atrial fibrillation, and other comorbidities have not yet been fully unraveled. This may partly be due to the interconnectedness of contractile, electrical and structural atrial remodeling.[40, 41] Rather than standalone events, these different types of remodeling create interconnected positive feedback loops, through which AF promotes AF. [42] Simultaneous observation or sampling of multiple remodeling processes may be necessary to elucidate the role of atrial fibrosis in AF.

Conclusion

Atrial fibrillation is a complex and multifactorial disease, and the pathogenesis of AF and underlying and contributing mechanisms remains incompletely understood. In this thesis, we present several clinical characteristics, electrical and structural remodeling processes that contribute to AF, and may affect the success of ablation strategies. The novel approach that we employ in this work is the truly translational combination of clinical characteristics with functional electrophysiological and histological changes in in-patient or in vitro tissue samples. How these translate into optimal treatment techniques and strategies remains disputed, especially for patients with persistent AF. A combination of basic, clinical and translational mechanistic research can put missing pieces of the AF-puzzle into place to unveil pivotal mechanisms that may act as potential treatment targets to enable effective and permanent elimination of AF.

Future perspectives

The mechanisms of AF pathogenesis remain incompletely understood, hampering the improvement of prognosis for patients with AF. Unraveling these mechanisms is complex due to the age-related progression and multifactorial etiology of AF. Identification of pivotal molecular pathways and biomarkers may improve the identification of patients at high risk of AF, and can act as future therapeutic targets. While this field of research is still under development, promising markers have been identified, such as primary cilia, several micro-RNA's, and factors produced by epicardial adipose tissue.[43-46] In addition, readily available data should be explored, such as clinically collected electrocardiograms. Machine learning techniques may identify unknown features of atrial fibrillation that could improve detection, or identify features previously unknown to predict AF.[47] Lastly, the increasing domestic use of wearable devices with heart rhythm recording capabilities provide new opportunities for the early detection of (subclinical) AF.

After the identification of subject at risk of AF, the next challenge is to prevent the actual arrhythmia. Risk factor management should be an integral part of prevention, as it is now an integral part of secondary prevention of recurrent AF.[1] Hypertension, heart failure, diabetes mellitus and sleep apnea are just some of these reversible risk factors. Some risk factors may require lifestyle changes, such as alcohol consumption, smoking and obesity. The research group from Adelaide demonstrated that AF may be reversible when risk factors are optimally treated, especially with regard to obesity. Subjects with ≥10 percent sustained weight loss experienced regression of symptoms and freedom of AF comparable to the effects of a catheter ablation.[48] Moreover, persistent AF may regress to paroxysmal form under intensive weight and risk factor management.[49] These studies demonstrate the reversibility of AF and the benefits of optimizing risk factors on the symptoms of AF and AF recurrence, and suggest that management of cardiovascular risk factors may beneficially change the atrial arrhythmogenic substrate.

Treatment strategy for patients with atrial fibrillation

The current guidelines recommend treatment of AF in the simple Atrial fibrillation Better Care (ABC) holistic pathway: (A) Avoid stroke, (B) Better symptom management, and (C) cardiovascular and comorbidity optimization.[1] In patients with more than one non-sex stroke risk factor (CHA_2DS_2-VASc score), anticoagulation therapy is indicated. Anticoagulation in these patients at increased risk of stroke improves survival.

Symptoms of AF can be managed with rate control. If rate control does not provide sufficient relief of symptoms, a rhythm control strategy may be applied. Rhythm control may be achieved with antiarrhythmic drugs. If symptoms of AF remain despite antiarrhythmic drug use, ablation is indicated. For patients with paroxysmal AF, pulmonary vein isolation alone is considered an effective treatment strategy. However, in patients with persistent or long-standing persistent AF, disappointing results led to the identification and ablation of several additional targets. Ablation of complex fractionated electrograms, linear ablation, rotor ablation and ganglion plexus ablation initially seemed promising, but failed to structurally improve the outcome of the procedure. [5, 50, 51] Contemporary ablation procedures are mainly performed with radiofrequency- or cryothermal ablation. Other techniques, such as microwave ablation and high intensity focused ultrasound ablation have

been developed, but were not sufficiently effective or safe.[52, 53] Laser balloon ablation appears sufficiently effective and safe, but is limited to PVI only.[54] The newest kid on the block, pulsed field ablation, so far has the potential to compete with RF and cryoablation. Pulsed field ablation causes electroporation, permanent damage of the cell membrane by application of strong electric field. Electroporation causes irreversible cell-death, which appears to be a tissue specific phenomenon without, or with limited thermal effects. Animal studies and preliminary studies in humans confirmed the feasibility and safety of this technique.[55-57] The long-term efficacy and safety remain to be determined, along with comparative trials with conventional RF ablation.

The optimal treatment strategy for AF remains unknown. Catheter ablation is considered effective in patients with paroxysmal AF. However, for patients with persistent AF, efficacy of catheter ablation is limited and recurrences and re-do procedures are common. Thoracoscopic ablation is more effective than catheter ablation, which comes at the cost of slightly more complications. [11, 58, 59] However, direct comparisons between these treatment modalities are sparse. The ongoing APPROACH AF trial is the first study to directly compare catheter and thoracoscopic ablation as a first approach, in patients with persistent AF. (NCT04715425). This landmark trial will guide cardiologists in the selection of patients for either thoracoscopic or catheter ablation with regard to efficacy, safety and cost-effectiveness.

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