Clinical, electrophysiological and structural aspects of atrial remodeling

Lessons from thoracoscopic ablation of atrial fibrillation

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Publication date
2023

Chapter 8

Summary

Atrial fibrillation is the most common cardiac arrhythmia, with an increasing incidence due to ageing of the general population. The increasing number of patients, frequent hospital visits and high (re)hospitalization rate impose a high burden on healthcare capacity and budgets. Atrial fibrillation is a complex, multifactorial and progressive disease. Despite modern therapeutic interventions, recurrences remain common. The pathophysiological processes in AF need to be unraveled to enable optimization of patient selection and treatment. Therefore, the aim of this thesis was to identify clinical, electrophysiological and pathophysiological characteristics associated with recurrent AF after thoracoscopic ablation.

Part 1: Clinical aspects of atrial remodeling

In **chapter 2** we analyzed the differences between women and men undergoing thoracoscopic ablation. Women referred for thoracoscopic ablation were four years older than men, and had fewer cardiovascular risk factors, fewer myocardial infarctions and fewer vascular disease. After two year follow-up, women had more 15% more recurrences than men, which was driven by a higher proportion of atrial tachycardia's as recurrence, with similar rates of AF. Sex was an independent risk factor for recurrent AF after correction for several established risk factors. Moreover, additional risk factors, such as persistent AF, old age and an enlarged left atrium, seem to impact females more severely than males. Upon histological analysis, women had more endo- and epicardial fibrosis compared to males, which may reflect a more progressed atrial substrate.

In **chapter 3** we assessed the efficacy of thoracoscopic ablation in patients with a giant left atrium, defined as LAVI (left atrial volume divided by body surface area) ≥ 50 ml/m^2. At baseline, patients with a giant left atrium were older and had more persistent AF. After two years follow-up, 43% of patients with a giant left atrium remained free from AF recurrence, compared to 57% in patients with a smaller LA. Subgroup analysis revealed that males with relatively small left atrium have the highest efficacy after ablation, whereas the efficacy was similar for both sexes in the presence of a giant LA. Similarly, patients with paroxysmal AF and a small LA had the highest efficacy, while patients with persistent AF had similarly lower efficacy with or without giant LA. Procedural related serious adverse events were similar for both groups.

Previously published studies were ambivalent about the risk of a previously failed catheter ablation on recurrence after thoracoscopic ablation. **Chapter 4** describes the results of a retrospective international multicenter trial comparing the efficacy of hybrid thoracoscopic ablation between patients with a failed catheter ablation and ablation naïve controls. At baseline, patients with a failed catheter ablation had smaller left atria, less congestive heart failure and less persistent AF. Patients with a failed catheter ablation had 2,5 years longer duration of AF. Two propensity score based analyses demonstrated a 39 and 68% increased risk of recurrence for patients with a previously failed catheter ablation compared to ablation naïve patients during one year follow-up. A failed ablation thereby acts as a marker for reduced efficacy. In a subgroup of patients, the density of collagen fibers was higher in patients with a failed catheter ablation, suggesting that these patients suffer from more progressed, subclinical, atrial fibrosis formation.

Part 2: Electrophysiological aspects of atrial remodeling

In **chapter 5** we evaluated the invasively measured left atrial epicardial conduction time (LAECT) as marker for AF recurrence after thoracoscopic ablation of AF. In patients with persistent AF, the right pulmonary veins were isolated, and a partial roofline, connected to a trigone line were ablated. Conduction block of these lesions was confirmed. LAECT was defined as the time to local activation at one side of the roofline upon pacing from the opposite side. LAECT was longer in older patients, in patients with a high body mass index, and in patients using class IC antiarrhythmics. Moreover, long LAECT, high BMI and a previously failed catheter ablation were independently associate with AF recurrence. Measurement of LAECT as invasive electrophysiological marker depends upon an isolated roofline, and its clinical applicability is thereby limited. This issue is overcome by high density epicardial mapping of atrial fibrillation in **chapter 6**. This technique enables electrogram analysis and reconstruction of the AF wavefront. We demonstrate that the complexity of AF increases with supposed progression from paroxysmal to persistent AF. We expressed the complexity of AF as AF cycle length, wavefront velocity, no of breakthrough waves and fractionation index. The complexity of AF was higher in persistent compared to paroxysmal AF. Moreover, AF was more complex in patients with ongoing AF compared to patients in sinus rhythm at the start of the procedure, in whom AF was induced with high frequency stimulation. These measurements confirm a concurrence of the complexity of the AF activation patterns with structural and electrical remodeling. Moreover, an increased difference in AF cycle length between the left and right atrium was associated with increased recurrence of AF. The complexity of AF thereby reflects electrical and structural remodeling of the atrial substrate.