Modulation of atrial fibrillation
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Summary
Chapter 1 reviews the epidemiology, risk factors and symptomatology of atrial fibrillation, the history of the underlying mechanisms of atrial fibrillation and the history of surgery for atrial fibrillation.

Many consider the classical Maze III procedure as the most successful treatment and the golden standard for the treatment of drug-refractory symptomatic atrial fibrillation. It was the first procedure that could overcome the thrombogenic, arrhythmogenic and partially the negative hemodynamic effects of atrial fibrillation. In Chapter 2 we show that the classical Maze III procedure is safe and effective for both atrial fibrillation without and with underlying structural heart disease (lone and concomitant atrial fibrillation). In a cohort of 203 consecutive patients who underwent a Maze III procedure no in-hospital mortality was noted. Freedom from atrial fibrillation after a mean follow-up of 4 years was 90% and 69% for patients who underwent a Maze III procedure for lone and concomitant atrial fibrillation respectively. None of the patients who underwent a Maze III procedure suffered from a stroke during follow-up.

Because the classical Maze III procedure is a complex and time-consuming operation, different modified Maze procedures have been developed over years. These modified Maze procedures differ in the lesion set and/or technique of creating non-conductive lines. Chapter 3 describes a cohort of 66 patients with mainly concomitant atrial fibrillation who underwent either a pulmonary vein isolation only, a left atrial Maze or a bi-atrial Maze procedure. While a left atrial Maze and bi-atrial Maze procedure are quite successful, pulmonary vein isolation only was not.

Surgical therapy for lone atrial fibrillation has been focusing on the pulmonary veins after the recognition that ectopic foci, originating from the pulmonary veins, play an important role in the pathophysiology of atrial fibrillation. The Sint Antonius Hospital in Nieuwegein was one of the first centers who performed a completely thorascopic isolation of the pulmonary veins in combination with ganglionic plexus ablation for lone atrial
fibrillation. **Chapter 4** describes the results of the first 30 patients treated in this way for lone atrial fibrillation. After a follow-up period of almost a year, the mortality was 0% and 77% of the patients were free from atrial fibrillation. Two patients required a conversion to a sternotomy to control bleeding. The mean hospital stay was 5 days. This shows that a completely thoracoscopic pulmonary veins isolation with ganglionic plexus ablation is a safe and effective procedure. This minimal invasive approach for lone atrial fibrillation has made the classical Maze III procedure almost completely obsolete in the treatment of drug-refractory symptomatic atrial fibrillation.

The success of the surgical therapy of atrial fibrillation and of the Maze III procedure in particular depends on the left atrial diameter. The bigger the left atrium, the smaller the chance of a successful outcome. Especially in case of mitral valve pathology the diameter of the atrium is large and surgery for atrial fibrillation is less successful. This is probably due to the presence of a larger arrhythmogenic substrate. Because fibrosis plays an important role in establishing the arrhythmogenic substrate, we have scored the amount of fibrosis in different groups of patients. **Chapter 5** shows that the left and right atrial appendages of patients with atrial fibrillation in combination with mitral valve disease contain more fibrosis than the appendage of patients with atrial fibrillation without mitral valve disease. Appendages of patients with lone fibrillation did not contain significantly more fibrosis than controls. Overall, right atrial appendages contained more fibrosis than left atrial appendages.

The importance of the autonomic nervous system in the pathophysiology of atrial fibrillation has been underscored years ago by Coumel and recently physicians are targeting the ganglionic plexus in the treatment of atrial fibrillation. The ‘classical’ neurotransmitters of the autonomic nervous system are noradrenalin and acetylcholine. **Chapter 6** describes the effect of these 2 ‘classical’ neurotransmitters at a concentration of 1µM on the action potential of isolated left atrial cells and of sinus node
cells of rabbits. Both acetylcholine and noradrenalin increase the maximal diastolic potential (hyperpolarization) and increase the maximum upstroke velocity of isolated left atrial rabbit myocytes. While noradrenalin increases the action potential duration at 90% of repolarization ($\text{APD}_{90}$), acetylcholine shortens it. The effect of noradrenalin on the action potential of sinus node cells was a decreased cycle length and an increased maximal diastolic potential (hyperpolarization) and the opposite was the case for acetycholine.

Apart from the ‘classical’ neurotransmitters noradrenalin and acetylcholine, the atria contain many more neurotransmitters. Chapter 7 describes the effect of various neurotransmitters on the action potential characteristics of isolated left atrial rabbit myocytes. While Neuropeptide-Y, Somatostatin-14 and Vasoactive Intestinal Peptide did not elicit an effect on the action potential, Substance-P (1 µM) increased the action potential duration and decreased the maximum diastolic potential (depolarization). The effect on the action potential duration was dose dependent and present at the tested frequencies of 1-4 Hz. The voltage clamp experiments suggested that a non-specific current, probably a potassium current, is responsible.

In this thesis we have investigated the results of various surgical procedures for atrial fibrillation which have been performed in the last 2 decades in the Sint Antonius Hospital, Nieuwegein, The Netherlands. In the 1990s the classical Maze III procedure was the main surgical technique for drug-refractory symptomatic lone atrial fibrillation at the Sint Antonius Hospital. A better understanding of the pathophysiology of atrial fibrillation has enabled an evolution in the surgical treatment of atrial fibrillation. Nowadays a completely thoracoscopic procedure is the main surgical therapy for lone atrial fibrillation at the Sint Antonius Hospital. Because knowledge and therapy of atrial fibrillation go hand in hand, this thesis deals also with the structural and humoral remodeling associated with atrial fibrillation, in particular with the amount of atrial fibrosis in patients with and without atrial fibrillation.
and with the electrophysiological effects of different neurotransmitters. This may help in developing more effective and probably tailored, patient specific and mechanism (substrate/trigger) specific, therapeutic procedures for atrial fibrillation.
Chapter 8

References:


