Modulation of atrial fibrillation
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GENERAL INTRODUCTION AND OUTLINE OF THESIS
Epidemiology, risk factors and symptoms of atrial fibrillation

Atrial fibrillation is the most common sustained arrhythmia with an overall prevalence of 5.5% above 55 years of age.\textsuperscript{1} In the USA alone it is estimated that a total of 2.3 million citizens suffer from atrial fibrillation and that this number will increase with time.\textsuperscript{2}

The prevalence of atrial fibrillation is strongly correlated with age and has a prevalence of almost nil before 55 years, but of almost 10% above 80 years of age.\textsuperscript{1-3} Other risk factors for atrial fibrillation are diverse and include heart failure, male gender, diabetes, coronary artery disease, valvular heart disease and hypertension.\textsuperscript{3-8}

The main symptoms of atrial fibrillation are palpitations, fatigue, vertigo, chest pain, dizziness, syncope and dyspnea. Not all patients do, however, experience symptoms.\textsuperscript{5,9} Even in patients who do experience symptoms of atrial fibrillation, episodes of atrial fibrillation are more often asymptomatic than symptomatic.\textsuperscript{10}

Atrial fibrillation can not only cause discomfort to the patient, but also imposes great health risks. Common symptoms are caused by a combination of an (fast) irregular heartbeat and a decreased cardiac output. This can lead to heart failure via 2 mechanisms. One is a direct effect caused by a decreased ventricular filling due to a decreased atrial contractile function and a shortening of diastolic ventricular intervals.\textsuperscript{11} The second mechanism is an indirect effect caused by remodeling due to prolonged high ventricular rhythm, which reduces systolic function (tachycardiomyopathy).\textsuperscript{12} Indeed, patients with atrial fibrillation have a 3 times increased risk of heart failure.\textsuperscript{13} Furthermore, atrial fibrillation is associated with a 5 times increased risk of ischemic stroke due to functional stand-still of the atria.\textsuperscript{14} In addition, strokes caused by atrial fibrillation are more lethal than non-AF related strokes.\textsuperscript{15} Recent studies also show that atrial fibrillation is an independent risk factor for dementia.\textsuperscript{16,17}

Overall, atrial fibrillation causes decreased quality of life, increased morbidity and is even an independent risk factor for death. It is responsible for a relative mortality risk of 1.5 in men and 1.9 in women from an age of 55 years.\textsuperscript{18}

Historical perspective of the mechanisms of atrial fibrillation

During the last few decades progress has been made in understanding the mechanism of initiation and maintenance of atrial fibrillation. This increased
knowledge of the mechanisms behind atrial fibrillation in combination with the low efficacy of pharmacological treatment and the associated life threatening drug induced arrhythmias in the form of Torsades de Pointes, has led to enormous progress in the non-pharmacological treatment of atrial fibrillation.\textsuperscript{19-21} To get a clear understanding of this progress it is necessary to know the historical perspective of the mechanisms of atrial fibrillation.

In the early 1900s, three main theories existed on the underlying mechanism of atrial fibrillation. These theories encompassed the presence of one or multiple rapid autonomic foci or reentry.\textsuperscript{22-24} In 1924 Garrey and co-workers recognized that a minimum amount of tissue (‘critical mass’) is necessary to maintain atrial fibrillation.\textsuperscript{25} This observation refuted both a single autonomic focus as well as multiple autonomic foci as a main cause of atrial fibrillation, and supported the concept of reentry being the underlying mechanism. Some years earlier, reentry had already been described by Mayer in jellyfish and later also in myocardium of tortoises and frog by Mines.\textsuperscript{26,27} The observed reentrant activations were always dependent on an anatomical obstacle and became known as \textit{circus movement reentry} (figure 1, figure 2A).\textsuperscript{24}

\textbf{Figure 1.} \textit{Circus movement reentry as it was originally describes by Lewis.}\nAt the bottom of the circle the tissue is stimulated (circle 1). At point A, a unidirectional block prevents clockwise conduction, but conduction is continued in counter-clockwise manner (circle 2). When the activation front has reached point A (circle 5), the tissue at this point has been repolarized and reentrant activation ensues.\nReproduced with permission from the publisher\textsuperscript{24}
A new concept of atrial fibrillation was proposed in 1959 by Moe and Abildskov and is known as multiple wavelet theory (figure 2B). Moe and co-worker hypothesized that multiple activation fronts (which they called ‘wandering wavelets’) are present during atrial fibrillation and that they continuously change in direction, size and number. They also hypothesized that the stability of the arrhythmia increases with a larger number of wandering wavelets, which would decrease the chance of simultaneous termination of all wandering wavelets. The number of wandering wavelets would depend on the tissue mass, conduction velocity and refractory period. A larger tissue mass can potentially harbor more wavelets, while a slower conduction velocity and a shorter refractory period allow smaller reentry circuits and thus more wandering wavelets in the same volume of tissue. The smallest possible reentry circuit can be expressed as the wavelength, which is a multiplication of the conduction velocity and refractory period. In 1964, the feasibility of the multiple wavelet theory as an underlying mechanism of atrial fibrillation was confirmed by a computer model and the mechanism was later confirmed by detailed activation mapping of atrial fibrillation in a canine model.

**Figure 2. Mechanisms of reentry and atrial fibrillation.**
Schematic drawing of different mechanisms of reentry. A: Circus movement reentry. This reentry occurs around an anatomical obstacle and because the length of the pathway is dependent on the circumference of the obstacle, which is larger than the wavelength, an excitable gap is present. Due to the excitable gap, this form of reentry can be entrained by pacing. B: Multiple wavelet theory. During atrial fibrillation multiple wandering activation wavelets are present. C: Leading circle reentry. The reentry is not dependent on an anatomical obstacle and because it will adapt to the smallest possible reentrant circuit (wavelength) there is no excitable gap and thus cannot be entrained. The center of reentry is kept continuous in a refractory state due to continuously invading activation fronts D: Spiral wave reentry. It strongly resembles the leading circle reentry, but the core (black dot) is not refractory like the leading circle reentry. The core is excitable, but not excited.
When the activation pathway is the same in every cycle of the arrhythmia, sequential mapping can be applied to map the activation path. Sequential mapping requires a single roving probe (electrode) and is technically less challenging than simultaneous mapping with large electrode grids and multichannel data acquisition systems. Until the 1970s sequential mapping techniques only permitted the demonstration of reentry with a fixed activation pathway around an anatomical obstacle (circus movement reentry). In 1973, Allessie and co-workers were, however, able to provoke and map functional reentry in atria of rabbit hearts, which led to a flutter-like tachycardia. This reentry mechanism became known as the leading circle reentry (figure 2C). The reentrant activation pathway of a leading circle reentry forms a circle which not only activates the surrounding tissue, but keeps the core refractory. The latter is caused by a continuously invasion of the core by activation fronts from all directions. The leading circle will adopt the smallest possible activation pathway (wavelength) and, in contrast to circus movement, almost no excitable gap is present (figure 2A and 2C).

Apart from circus movement reentry, multiple wandering wavelets and leading circle reentry, a fourth reentry mechanism has been suggested as a mechanism for atrial fibrillation. A spiral wave reentry (figure 2D) is a form of functional reentrant activation and strongly resembles the leading circle reentry. The main difference between a leading circle reentry and a spiral wave reentry is the state of the core. While the core of the leading circle is thought to be continuously refractory, the core of a spiral wave is excitable but is not excited.

Until the late 1990s, non-pharmacological treatment for atrial fibrillation was mainly based on reentry as the prime mechanism of atrial fibrillation. This changed substantially when Haïssaguerre and co-workers revealed that atrial fibrillation was initiated by ectopic foci originating from the myocardial sheaths of the pulmonary veins, and that ablating these foci could terminate atrial fibrillation. From that time onward, non-pharmacological therapy for atrial fibrillation focused more on modification of the triggering mechanisms in the pulmonary veins.

Until today, the exact underlying mechanisms of atrial fibrillation remain unknown. Independent of the exact mechanism or mechanisms of atrial fibrillation, the arrhythmia can, however, be considered as a condition which is initiated by triggers, maintained or realized by the substrate and influenced by modulating
Trigger and substrate of atrial fibrillation

The trigger is the initiator of the arrhythmia, while the substrate harbors or maintains the arrhythmia. The mechanisms behind the triggers (or foci) that initiate atrial fibrillation are not known. Abnormal automaticity, triggered activity and micro-reentry are the three major possibilities that have been postulated as mechanisms for these focal activations.

The possibility of automaticity as a mechanism for ectopic foci came from the observation of Brunton and Fayer in 1876. They saw that the pulmonary veins could contract independently from the rest of the heart. This observation suggested that pulmonary veins contain myocardial cells that harbor pacemaker properties. Later studies showed indeed that the pulmonary veins in both animals and humans are excitable and contain sleeves of atrial myocardial cells and that some cells strongly resemble sinus node cells. Furthermore, spontaneous diastolic depolarization, a pacemaker property, was recorded in pulmonary vein myocardium of dogs. Whether automaticity really leads to atrial fibrillation remains unclear.

Another possible mechanism for ectopic foci is triggered activity. Triggered activity is a condition when a normal action potential is followed by depolarization of the membrane which reaches the activation threshold and leads to an action potential. Two different types of these membrane depolarizations exist, early after depolarizations (EADs) and delayed after depolarizations (DADs). An EAD is an abnormal transient depolarization of the membrane (potential) during phase 2 or 3 of the action potential. The exact mechanism behind an EAD remains a topic of debate. Two main mechanisms seem to play a role. The first is a transient inward current due to re-activation of the L-type calcium channels. The second is spontaneous Ca$^{2+}$ release from the sarcoplasmic reticulum under conditions of elevated diastolic intracellular Ca$^{2+}$ concentrations. In the latter case, the excess Ca$^{2+}$ is removed from the cell through the Na$^+$/Ca$^{2+}$-exchanger, generating a net inward current by exchanging 3 Na$^+$-ions for 1 Ca$^{2+}$-ion. The DAD is an abnormal transient depolarization of the membrane (potential) during phase 4, when the membrane is completely repolarized. In contrast to EADs, general consensus exists on the mechanism of DADs. This mechanism is similar to one of the proposed...
mechanism of an EAD: generation of a net inward current by the Na\(^+\)/Ca\(^{2+}\)-exchanger under conditions of elevated diastolic intracellular Ca\(^{2+}\).\(^{49,50}\)

Micro-reentry has been suggested as a third mechanism of ectopic activation initiating atrial fibrillation because of the distinctive structure of the pulmonary veins. Sleeves of myocardium reach up to 2 cm into the pulmonary veins and have a criss-cross fiber direction.\(^{51,52}\) Additionally, an increased amount of fibrous tissue is found in the pulmonary veins of patients with atrial fibrillation.\(^{53}\) These two characteristics of the pulmonary veins can lead to severe conduction delays and block.\(^{54,55}\) The severe conduction delay can potentially result in an extremely short wavelength (micro-reentry), while the highly anisotropic tissue characteristics favor unidirectional conduction block and thus reentry.

**Modulating factors**

In 1987, Coumel already stated that apart from the simultaneous presence of a trigger and substrate, a third factor, the modulating factor, is necessary in the genesis of an arrhythmia (figure 3).\(^{40}\) He proposed that the autonomic nervous system could act as an important modulating factor.\(^{40}\) This concept of a trigger, substrate and modulating factor is schematically depicted in figure 3 and is known as the Triangle of Coumel (figure 3). To date, this trinity of a trigger, a substrate and a modulating factor is the leading concept of atrial fibrillation.

![Triangle of Coumel](image)

**Figure 3. Triangle of Coumel**
The triangle of Coumel schematically depicts the trinity of a substrate, trigger and modulating factor. This trinity is responsible for atrial fibrillation (AF).
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Other modulating factors, different from the autonomic nervous system, exist. Endothelial dysfunction, inflammation, hormonal factors, obesity and atrial stretch have all been suggested to modulate arrhythmogenesis. The main modulating factor is, however, probably atrial fibrillation itself. This phenomenon is generally described as ‘atrial fibrillation begets atrial fibrillation’ after the publication by Wijffels and co-workers of a goat model of AF. They demonstrated that when atrial fibrillation was continuously re-induced by atrial pacing (in healthy goats), the arrhythmia became self-sustainable due to shortening of the refractory period. Indeed, while the onset of atrial fibrillation in man is often paroxysmal in nature, it becomes eventually persistent or even permanent. In addition to electrical remodeling, atrial fibrillation is also associated with structural and contractile remodeling, which may add to the arrhythmogenic vulnerability of the substrate.

Electrophysiological remodeling by atrial fibrillation in the form of a decreased refractory period has been a consistent finding. The decreased refractory period caused by atrial fibrillation is the result of shortening of the action potential mainly by a decreased L-type Ca\(^{2+}\) current and an increased inward rectifying K\(^+\) current (\(I_{K1}\)).

Structural remodeling observed in subjects with AF is diverse and, in part, consists of atrial dilatation, increased cell-size, myolysis, perinuclear accumulation of glycogen, alterations in connexin expression, fragmentation of sarcoplasmic reticulum and changes in mitochondrial shape. The clinical relevance of these structural changes remains, however, unknown.

Logan and co-workers were the first who recognized loss of contractile function. They observed that immediately following electrical cardioversion the left atrium lacked contraction despite activation. Subsequent echocardiographic studies confirmed that atrial contractility was diminished after termination of atrial fibrillation and that the time of complete recovery of contractility depended on the duration of atrial fibrillation before the electric cardioversion.

The exact mechanism for this phenomenon is not fully understood. Various studies, however, suggest that a decreased intracellular calcium concentration resulting from a reduced L-type Ca\(^{2+}\) current is the culprit process.
Chapter 1

Fibrous tissue and atrial fibrillation

It is generally believed that atrial fibrosis plays an important role in atrial fibrillation. While there is a clear relation between atrial fibrosis and atrial fibrillation, the causality between the two is less clear.

Both experimental and clinical studies have shown a relation between atrial fibrillation and fibrosis. In man, an increased amount of fibrous tissue is found in atria of patients with atrial fibrillation compared to those of patients in sinus rhythm and of patients with mitral valve disease compared to those without mitral valve disease. Furthermore, mice with increased amounts of fibrous tissue, due to genetically overexpressing TGF-β1, are more vulnerable to atrial fibrillation.

The increased amount of fibrous tissue observed in patients with atrial fibrillation could be due to structural remodeling. However, the increased amount of fibrous tissue could also have a different origin and be the cause instead of the result of atrial fibrillation. Fibrosis itself may provide the substrate for reentry and thus for atrial fibrillation in two manners. One is ‘current-to-load mismatch’ and the other anisotropic or ‘zigzag’ conduction.

Fibrosis can create nonconductive barriers that can cause conduction delay and block via so-called current-to-load mismatch. Fibrotic barriers cause variation in the tissue architecture. At sites of tissue expansion more depolarizing current is required for successful propagation. At these sites conduction delay may arise and finally lead to conduction failure if the available depolarizing current is insufficient. This form of conduction block depends on the spatial variation within the myocardium and is therefore often unidirectional in nature and thus favors unidirectional block which is necessary for reentrant arrhythmias like atrial fibrillation. The second mechanism by which fibrosis makes the substrate more susceptible for atrial fibrillation is due to ‘zigzag’ conduction. The nonconductive barriers caused by fibrosis causes the activation front to travel around these barriers by creating a ‘zigzag’-like path, which results in prolongation of the activation time in mainly the transversal direction. This causes increased anisotropic conduction which favors reentry and thus atrial fibrillation.

Autonomic nervous system and atrial fibrillation

In 1987, Coumel already recognized that the autonomic nervous system plays a key role
in atrial fibrillation. He recognized that especially paroxysmal atrial fibrillation is dependent on a dysbalance of the autonomic nervous system. He described both vagally and adrenergically induced atrial fibrillation. Vagally induced paroxysmal atrial fibrillation is often preceded by a bradycardia and occurs predominantly at night. This type of paroxysmal atrial fibrillation is mainly seen in patients without structural heart diseases. Adrenergically driven atrial fibrillation is less common and is often secondary to a cardiac disorder. This type of atrial fibrillation occurs typically at daytime during exercise or stress and often coexists with structural heart disease. A large observational study in Europe led to the identification of the onset of atrial fibrillation either as vagal or as adrenergic in 33%. Vagally-only induced atrial fibrillation was present in 6% of the patients, adrenergically-only in 15% and the remainder (12%) had a mixed pattern. Surprisingly, the prevalence of structural heart diseases did not differ between patients with vagal and adrenergic induced atrial fibrillation.

The intrinsic nervous system of the heart is a complex system of ganglionic plexus, which at the atrial level are predominantly located in the fat pads around the pulmonary veins. Each ganglion can contain several hundreds of neurons. These neurons contain not only acetylcholine and noradrenalin, but many other neurotransmitters such as substance-P.

It has become clear that the autonomic nervous system can exert a large effect on the electrophysiological properties of the atria. Both vagal and adrenergic stimulation shorten the atrial refractory period and thus allow shorter wavelengths favoring reentry. Many animal models of atrial fibrillation use some form of vagal stimulation to initiate and maintain atrial fibrillation. The susceptibility for atrial fibrillation during vagal stimulation is thought to be caused not only by the shorting of the refractory period, but also by an increased dispersion of refractoriness.

Only in the last years cardiologists and cardiac surgeons have gained special interest in the autonomic nervous system in atrial fibrillation. This is for a large part caused by seminal work of the group from Oklahoma. They have shown which drastic effects the autonomic nervous system can have on both the substrate and the initiating factor. At present, some non-pharmacological therapies not only target the myocardial sleeves of the pulmonary veins, but also attempt to modify the atrial autonomic nervous system. Both surgical epicardial and percutaneous
endocardial procedures are combining pulmonary vein isolation with ablation of ganglionic plexus. 85-87

From experimental and clinical studies it appears that targeting the autonomic nervous system can be beneficial in the treatment of atrial fibrillation. 83,86,88,89 However, no randomized trials which compare pulmonary vein isolation with or without ganglionic plexus ablation have been published.

History of surgery for atrial fibrillation
Due to low efficacy of anti-arrhythmic medication in maintaining sinus rhythm and the side effects of both anti-arrhythmic and anti-coagulant medication, surgical procedures were developed for the treatment of atrial fibrillation in the late 1980s and early 1990s. Two of the first surgical treatments were the Corridor and the Maze procedures. Although the Maze procedure was very successful, many various surgical approaches were in use and developed over time and some are described below.

Left atrial isolation and Corridor procedure
In 1980, the ‘left atrial isolation’ was described and was the first surgical procedure for atrial fibrillation. 90 It was originally designed to treat autonomic or ectopic supraventricular tachycardias originating from the left atrium (figure 4). The procedure electrically isolated the left atrium from the right atrium, thereby prevented tachycardias originating from the left atrium from conducting to the right atrium. This procedure appeared also to be beneficial for atrial fibrillation. After the procedure was performed for atrial fibrillation, the sino-ventricular co-ordination was restored, but the left atrium continued to fibrillate or became electrically silent.

The ‘Corridor’ procedure was described by Guiraudon in 1985. 91 It surgically created an electrical isolated corridor from the sinus node to the AV-node (figure 5). Like the left atrial isolation procedure, it restored the sino-ventricular co-ordination, but both the left and right atrium continued to fibrillate. This procedure was considered as an alternative for pacemaker implantation after His-ablation for drug-refractory atrial fibrillation. 92 Its advantage over pacemaker implantation is that the ventricles are physiological paced by the sinus node instead of a pacemaker.

Both the Corridor procedure and the left atrial isolation procedure
have a success rate of approximately 70-80% in restoring the sino-ventricular co-ordination\textsuperscript{92-95} However, the risk of thrombo-embolism remains due to the loss of atrial systolic function and thus patients remain dependent on anti-coagulation therapy.

\textbf{Figure 4.} \textit{Left atrial isolation procedure.}\n\begin{flushright}
Drawing of the left atrial isolation procedure. This procedure electrically isolates the left atrium from the right atrium. (LAA= left atrial appendage, CS= coronary sinus, MV= mitral valve).
\end{flushright}
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\textbf{Figure 5.} \textit{Corridor procedure.}\n\begin{flushright}
Schematic overview of the Corridor procedure. The procedure surgically creates a small path of tissue (‘Corridor’) from the sinus node (arrow) to the AV-node. This electrically isolated path prevents reentry and thus atrial fibrillation within the path. This restores sino-ventricular co-ordination, but the left and right atrium remain susceptible for atrial fibrillation. (PV= pulmonary vein, MI mitral valve circumference, TRI = tricuspid valve circumference)
\end{flushright}
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**Chapter 1**

*Maze procedure*

The Maze operation was the first treatment of atrial fibrillation which could overcome all negative effects of atrial fibrillation and was designed by Cox and co-workers in the late 1980s. In contrast to the Corridor and left atrial isolation procedures, the Maze not only restored the sino-ventricular co-ordination, but also reduced the risk for thrombo-embolism and restored atrial contractility.

The development of the Maze procedure was based on the *multiple wavelet theory* and reentry as the mechanism of atrial fibrillation. Cox and co-workers recognized that preventing or disrupting these reentrant activities could prevent atrial fibrillation. The objective of the Maze procedure was to create a labyrinth (hence Maze) of non-conductive lines in the atria, with the sinus node as entrance and the AV-node as exit. These non-conductive lines were created in a fixed pattern in both atria by cutting and sewing (figure 6).

The initial Maze procedure which was performed on man (now called Maze I) led in many patients to sinus node dysfunction. It was therefore modified to the Maze II and eventually to the Maze III procedure (figure 6). The Maze III procedure became a well-accepted and widely used therapy for drug-refractory symptomatic atrial fibrillation and was long-time considered as the golden standard for non-pharmacological treatment of atrial fibrillation.

*Modified Maze procedure*

Despite its high success rate, the Maze III operation was not widely adopted and the classical ‘cut-and-sew’ method is nowadays almost totally abandoned. The reason was that the procedure is time consuming, technically challenging, requires a sternotomy and involves the use of extra-corporeal circulation. Especially for lone atrial fibrillation, the morbidity and mortality caused by the operation is large in comparison to the gravity of the disease.

Not only disadvantages inherent to the Maze operation, but also the development of ablation devices that were able to create lines of non-conductive tissue, changed surgery for atrial fibrillation. These ablation devices replaced the time consuming ‘cut-and-sew’ technique and led amongst others to the Maze IV procedure. This procedure strongly resembled the Maze III procedure, but uses mostly radiofrequency ablation to create the lines of non-conductive tissue.
The Maze III procedure creates a labyrinth in the atria by a fixed pattern of lines which are created by cutting and sewing the myocardium.

At the top the incisions in the right atrium are depicted. First the right atrial appendage is amputated. From this a short perpendicular incision in the free wall is made and an incision to the tricuspid annulus which is completed by a cryo-lesion. This is followed by an atriotomy between the superior caval and inferior caval vein. From this incision a second incision to the tricuspid annulus is made and also completed by a cryo-lesion. Finally a septal incision is made to provide access to the left atrium.

At the bottom the incisions in the left atrium are depicted. First, the left atrial appendage is amputated. The septal incision is extended to form a button around the pulmonary veins and is connected to the incision of the amputation of the left atrial appendage. From the button an incision to the mitral valve annulus is made and completed with a cryo-lesion.

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The last factor that led to further abolishment of the Maze III procedure is our understanding of atrial fibrillation. The Maze III operation was totally based on the idea that atrial fibrillation existed of multiple wandering reentry wavelets. In fact Cox and co-workers wrote: “Despite these observations, the erroneous concept that atrial fibrillation was caused by multiple autonomic foci persisted in the medical literature for the next 35 to 40 years”. While during atrial fibrillation multiple reentry wavelets are indeed presents, the importance of autonomic foci became clear in the late 1990s when Haïssaguerre and co-workers showed the importance of ectopic foci located in the pulmonary vein. From that time onward, both cardiologist and cardiac surgeons focused on the pulmonary veins in the treatment of, especially, lone paroxysmal atrial fibrillation.

Many variations on the classical Maze procedure have been in use since the development of the Maze III procedure. These variations included both the type of ablation technique and the pattern of (ablation) lines. Different studies suggest that these modified procedures are as effective as the classical Maze III procedure.

**Pulmonary vein isolation**

A broad scala of different techniques of percutaneous catheter ablations have been reported. Some even mimic parts of the Maze procedure. While the long-term success of surgery for atrial fibrillation is well established, the long-term success of catheter ablations for persistent atrial fibrillation remains controversial. While percutaneous catheter techniques are often the first choice for drug-refractory symptomatic atrial fibrillation, new minimally invasive surgical techniques have been developed. Surgical isolation of the pulmonary veins has 3 major advantages compared to catheter based ablation. First, surgical epicardial ablation is performed under direct vision, while endocardial is dependent on navigation systems and fluoroscopy. Second, ganglion plexus can be detected and ablated. Third, the left atrial appendage can be amputated, which is thought to be an important source of thrombo-emboli.

In 2005 Wolf and co-workers described a minimally invasive procedure during which they isolated the pulmonary veins by bipolar radiofrequency ablation, ablated the ganglionic plexus and amputated the left atrial appendage. This
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The technique was later modified to a completely thoracoscopic procedure.\textsuperscript{110}

Hybrid epicardial-endocardial approach

The thoracoscopic epicardial approach for atrial fibrillation has also some disadvantages. Confirmation of pulmonary vein isolation can be difficult, a ‘classical’ ablation line to the mitral valve annulus is not possible and confirmation of conduction block of additional lines is dependent on custom made catheters.\textsuperscript{87}

Recently, some groups are performing simultaneous epicardial and endocardial approaches to treat atrial fibrillation.\textsuperscript{111-113} First results are promising, but a clear disadvantage is that it needs a hybrid operation room which also harbors the possibility of fluoroscopy.

Concluding remarks

Over the last decades enormous progress has been made in understanding the pathophysiology and etiology of atrial fibrillation. Non-pharmacological therapy became successful after the development of the Maze operation in the 1990s. From then on an evolution of techniques and recognition of the importance of the pulmonary vein has led to a broad range of both surgical and catheter based therapies. Nowadays, both percutaneous endocardial and surgical epicardial ablation are highly successful for especially lone paroxysmal atrial fibrillation with limited peri-procedural morbidity.

Aim and outline of the thesis

This thesis is collaboration between the departments of cardiothoracic surgery of the Sint Antonius Hospital in Nieuwegein and Experimental Cardiology of the Academic Medical Center of Amsterdam.

The aim of the thesis was to assess the success of different surgical techniques as treatment of atrial fibrillation and to obtain a better insight in the role of fibrosis and autonomic nervous in atrial fibrillation. In Chapter 2, 3 and 4 we will address the question of the success rates of the classical Maze III procedure, of modified Maze procedures and of a completely thoracoscopic pulmonary vein isolation, respectively. In Chapter 5 we will address the question whether more fibrosis is present in atria of patients with concomitant atrial fibrillation than in atria of
patients with lone atrial fibrillation, and whether the left and right atria are equally affected. In Chapter 6 we will describe the effect of noradrenalin or acetylcholine on the action potential of atrial and automatic (sinoatrial nodal) cells. Finally, in Chapter 7 we will describe the electrophysiological effect and ionic mechanism of the neurotransmitter substance-P on single atrial myocytes.
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References:


50. Ter Keurs HE, Boyden PA. Calcium and arrhythmogenesis. Physiol Rev 2007;87:457-506


Chapter 1


68. Burstein B, Nattel S. Atrial fibrillation: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-809


General introduction and outline of thesis


74. Rohr S, Salzberg BM. Characterization of impulse propagation at the microscopic level across geometrically defined expansions of excitable tissue: multiple site optical recording of transmembrane voltage (MSORTV) in patterned growth heart cell cultures. J Gen Physiol 1994;104:287-309


84. He B, Scherlag BJ, Nakagawa H, Lazzara R, Po SS. The intrinsic autonomic nervous system in atrial fibrillation: a review. ISRN Cardiol 2012;2012:490674
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