Introduction

General introduction

Epidemiology
Atrial fibrillation is the most common cardiac arrhythmia increasing exponentially with age (Kannel 1982, Wolf 1987, Feinberg 1995). The estimated prevalence roughly doubles with each decade of advancing age, from 0.5% at age 50-59 years to almost 9% at age 80-89 years. Moreover, the prevalence seems to have increased in the past two decades, particularly in men (Kannel 1998). It should be noted that these epidemiological trends occur despite a decline of rheumatic heart disease in the Western world, a condition historically associated with the arrhythmia. Advancing age, hypertension, diabetes, heart failure, valvular heart disease, and male gender are other conditions independently associated with atrial fibrillation (Kannel 1982, Benjamin 1994, Psaty 1997, Kannel 1998). When the above mentioned numbers of the Framingham study (in out-patients) are translated to the Netherlands, as many as 121.800 people aged 50 to 89 years would suffer from atrial fibrillation in the year 2000 (based on 15.8 million inhabitants, 13.6% above 65 years of age (CBS 1998)). The yearly incidence of atrial fibrillation in this cohort would be about 21.200 cases. The Netherlands Heart Foundation has calculated a comparable prevalence of 127.308 patients for the year 1996 (Konings-Dalstra 1999), based on a model combining data from domestic and foreign studies (Lake 1989, Phillips 1990, Wolf 1991, Furberg 1994, Langenberg 1996, Ott 1997). Remarkably, no specific data on atrial fibrillation are available for the Netherlands at the Central Bureau for Statistics. However, with the expected “ageing” and increase of the Dutch population (16.6 million in the year 2010, 14.8% above 65 years of age (CBS 1998)), more people will be suffering from atrial fibrillation, putting an increasing demand on public health care. This scenario is supported by already more than a doubling of the number of hospital admissions for atrial fibrillation between the years 1980 and 1997 (Konings-Dalstra 1999).
Classification
The arrhythmia is not uniform in its presentation. Different temporal patterns, each requiring specific therapy, can be distinguished. Classically, atrial fibrillation has been divided in paroxysmal (in attacks) and chronic (continuous) atrial fibrillation. More recently, however, it has become clear that both types are to be considered as “chronic” since the first attack (or episode) will not be the last (Suttorp 1993, Van Gelder 1996). Still, the following patterns can be distinguished according to Gallagher and Camm: (a) atrial fibrillation occurring in episodes, predominantly lasting less than 24 hours and often self-terminating, (b) atrial fibrillation continuously present while sinus rhythm can be restored with cardioversion, and (c) permanent atrial fibrillation in which restoration of sinus rhythm is either not possible anymore or deemed unnecessary (Table 1).

<table>
<thead>
<tr>
<th>Classification of atrial fibrillation by temporal pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paroxysmal</strong></td>
</tr>
<tr>
<td>Episodes of atrial fibrillation typically &lt;24-48 hours (up to 7 days)</td>
</tr>
<tr>
<td>Intermittent sinus rhythm</td>
</tr>
<tr>
<td>Terminating spontaneously or with an antiarrhythmic drug</td>
</tr>
<tr>
<td><strong>Persistent</strong></td>
</tr>
<tr>
<td>Continuous presence of atrial fibrillation &gt;24-48 hours duration</td>
</tr>
<tr>
<td>Not spontaneously terminating</td>
</tr>
<tr>
<td>(Electrically) cardiovertible</td>
</tr>
<tr>
<td><strong>Permanent</strong></td>
</tr>
<tr>
<td>Continuous presence of atrial fibrillation &gt;24-48 hours duration</td>
</tr>
<tr>
<td>Not spontaneously terminating</td>
</tr>
<tr>
<td>Not cardiovertible (anymore)</td>
</tr>
</tbody>
</table>

Etiology
Atrial fibrillation is also not uniform with respect to concomitant disease. Although an associated disease which might trigger and sustain the arrhythmia is often present, an obvious etiology may be absent (“lone” atrial fibrillation). In persistent atrial fibrillation structural heart disease is present in ±85% of the patients. By contrast, in paroxysmal atrial fibrillation only 40-50% of the patients have structural heart disease (Murgatroyd 1993). Table 2 shows the distribution of underlying heart disease and other predisposing factors as
Introduction

Table 2. Distribution of common etiologies and predisposing factors in atrial fibrillation

<table>
<thead>
<tr>
<th>Underlying heart disease (%)</th>
<th>Paroxysmal AF*</th>
<th>Persistent AF*</th>
<th>Permanent AF*</th>
<th>Persistent AF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>12</td>
<td>19</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>17</td>
<td>25</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Rheumatic valvular disease</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>2</td>
<td>9</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Non-rheumatic valvular disease</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Idiopathic or “lone”</td>
<td>46</td>
<td>28</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other predisposing or associated factors (%)</th>
<th>Paroxysmal AF*</th>
<th>Persistent AF*</th>
<th>Permanent AF*</th>
<th>Persistent AF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
<td>46</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Bronchopulmonary disease</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>9</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14</td>
<td>18</td>
<td>43</td>
<td>36</td>
</tr>
</tbody>
</table>

* = adapted from Levy 1999. † = in 509 patients from our institute who entered serial electrical cardioversion therapy between 1995-1999. AF = atrial fibrillation.

recently found in a French study (Levy 1999), together with data from our own cardioversion population. When compared to nearly a decade ago (1986-1991), the distributions of hypertensive and rheumatic heart disease seem to have changed positions while coronary artery disease has remained unchanged (Van Gelder 1991b).

Consequences of atrial fibrillation
Although not immediately lethal once it occurs, the arrhythmia is not benign. Atrial fibrillation carries the risks of considerable morbidity and increased mortality.

Symptoms
With respect to symptomatology, the presentation of the arrhythmia is inconsistent. Although most patients have symptoms secondary to atrial
fibrillation, about 10% (or even more) have none (Levy 1999). The most frequently reported symptoms include palpitations, chest pain, dyspnea (on exertion), syncope, dizziness, and fatigue. Typical for the paroxysmal form is polyuria during or immediately after an attack, and fatigue, sometimes persisting for days after the attack. Up till now, the clinical significance of asymptomatic atrial fibrillation is not always clear. Essentially patients with tachycardio-myopathy lack symptoms of atrial fibrillation but have significant heart failure symptoms. Likewise, asymptomatic patients may suffer from cerebral thromboembolism and are identified as having atrial fibrillation in the neurology department. In line with these uncertainties, data on the impact of the arrhythmia (and subsequent treatment) on feelings of well-being and social functioning are sparse. However, measuring quality of life in patients with atrial fibrillation is important as it may guide us in the assessment of therapeutic choices.

**Thromboembolism**

A most serious complication is thromboembolism from the left atrium (usually from its appendage) to the cerebral vasculature, resulting in a “stroke”. In particular rheumatic atrial fibrillation is associated with a high risk for stroke (Wolf 1987). It is estimated that the yearly risk for stroke in non-rheumatic atrial fibrillation is 5-7%, and that the cumulative risk approaches 35% (Chesebro 1995). Stroke secondary to atrial fibrillation has a high lethality rate and survivors often suffer from persisting neurological impairment (Lin 1996). Importantly, cerebral damage while in atrial fibrillation may occur quite insidiously. In the absence of clinical stroke, a clear association with dementia and impaired cognitive function was observed (Ott 1997), possibly related to silent stroke (Petersen 1987). In the presence of structural heart disease or other risk factors, the probability for embolism rises (twofold or even higher) considerably (Wolf 1991, SPAF Investigators 1992a, SPAF Investigators 1992b). These factors comprise previous stroke or a transient ischemic attack, higher age, hypertension, clinical heart failure, diabetes mellitus, overt coronary artery disease, left atrial enlargement, and left ventricular dysfunctioning.

Large clinical trials have investigated the prevention of thromboembolism and demonstrated the efficacy of long-term oral anticoagulation, especially in older patients (>75 years) and in the presence of risk factors (AFASAK 1989,
BAATAF 1990, SPINAF 1990, CAFA 1991, SPAF I 1991, SPAF II 1994, SPAF III 1996). If aspirin is considered, its use should be limited to younger patients (<65 years) without risk factors (SPAF II 1994). The studies, however, indicate that thromboembolism still occurs in 1-3% of the patients per year despite anticoagulative therapy. Moreover, depending on anticoagulation intensity, bleedings are introduced (up to 2.5% per patient/year) with sometimes serious consequences. Nevertheless, anticoagulation should be instituted in any patient with risk factors and/or age >65 years independent of the type of atrial fibrillation, since all previously mentioned studies included both patients with persistent and paroxysmal atrial fibrillation. It is as yet unsettled whether patients with lone atrial fibrillation are at increased risk for thromboembolic events.

**Heart failure**

Another clinical complication of atrial fibrillation is the occurrence of heart failure. Several underlying mechanisms have been identified or postulated. Firstly, ventricular rate usually becomes high once atrial fibrillation occurs. As a consequence, diastolic filling time becomes relatively short, thus decreasing stroke volume. Secondly, the loss of atrial contraction lowers cardiac performance by ±15% (Naito 1983). Thirdly, the irregularity of ventricular rate per se, irrespective of rate, contributes to deterioration of ventricular function (Daoud 1996, Clark 1997). Finally, a sustained, high ventricular rate may produce tachycardia-induced cardiomyopathy (or tachycardiomyopathy). Lowering of ventricular rate (either by rate or rhythm control) improves or normalizes ventricular function (Van den Berg 1993, Van Gelder 1993, Brignole 1994), which is an essential feature of tachycardia-induced cardiomyopathy. It should be noted, however, that reversibility is lost once structural changes such as atrophy and interstitial fibrosis develop. Alternative concepts of heart failure in atrial fibrillation include progressive impairment of cardiac function due to an underlying disease or progressive atrial natriuretic peptide depletion (Van den Berg 1998). The mechanisms, however, behind the coexistence of heart failure in atrial fibrillation have not yet been fully elucidated.

**Mortality**

It is a subject of ongoing debate whether atrial fibrillation is associated with
increased mortality (Middlekauff 1991, Carson 1993, Krahn 1995, Stevenson 1995, Benjamin 1998, Dries 1998, Crijns 2000). The risk of dying is estimated to be doubled in the presence of atrial fibrillation, although stroke, underlying cardiac disease, and the presence of heart failure in particular are held responsible for this outcome. Still, recent data from the Framingham study suggest that after adjusting for underlying cardiovascular conditions, mortality remains (about 1.5 fold) excessive (Kannel 1998). Moreover, after long-term follow-up of patients with lone atrial fibrillation, total mortality appears to be (about twofold) increased (Jouven 1999). Consequently, reassuring a patient with atrial fibrillation (and few symptoms) is not justified on the basis of these data. Importantly, it is as yet unclear whether (permanent) restoration of sinus rhythm will normalize mortality rates.

Study rationale
The above mentioned considerations would be irrelevant if atrial fibrillation in general could be (easily) terminated and prevented. However, until now, this is not the case. Patients with the paroxysmal form often progress to the persistent form, which is to be regarded as progression of the disease (Petersen 1986). In turn, persistent atrial fibrillation tends to become permanent, in spite of intensive serial cardioversion and antiarrhythmic drug therapy (Crijns 1991, Van Gelder 1996). It was observed that underlying heart disease has a negative impact on arrhythmia outcome. In addition, a long history or duration of the arrhythmia carries a poor prognosis, which indicates that changes occur as a consequence of the arrhythmia itself (Van Gelder 1996, Duytschaever 1998).

In the past decade, experimental studies were initiated to gain more insight in the pathophysiology of atrial fibrillation. It was a landmark finding that atrial fibrillation, as a result of atrial fibrillation per se, contributes to its own perpetuation by means of "electrical remodeling" (characterized by shortening of the atrial refractory period and flattening, or even inversion, of physiological rate adaptation). In animal experiments, atrial electrical remodeling seems to be completed within several days (Morillo 1995, Wijffels 1995), and reversibility after restoration of sinus rhythm occurs within the same time-frame (Wijffels 1995, Garratt 1999). A comparable course of electrical remodeling and recovery
from electrical remodeling appears to occur in humans (Franz 1997, Pandozi 1998, Yu 1999). The clinical representation of the latter may be the high incidence of subacute arrhythmia recurrences (within the first week after cardioversion) due to a persisting arrhythmogenic substrate in conjunction with frequent premature atrial beats, serving as triggers (Tieleman 1998). Although electrical remodeling is important, it is not the only determinant of atrial remodeling. Particularly animal studies show that other changes occur after electrical remodeling. These changes include contractile (Manning 1994), (neuro)hormonal (Roy 1987, Jayachandran 2000), and in particular (ultra)structural cellular adaptive processes (Ausma 1997, Gaspo 1997, Van Wagoner 1997, Yue 1997, Brundel 1999, Van Gelder 1999, Van Wagoner 1999, Brundel 2000). Comparable to electrical remodeling, it may be surmised that these processes are dysfunctional, eventually facilitating arrhythmia persistence.

At present, it is insufficiently understood what factors determine atrial remodeling and (subsequent) arrhythmia intractability in the clinical setting. First, human atrial fibrillation apparently occurs spontaneously. Thus, triggers, substrate, and modulating factors (for instance abnormal autonomic influences) presumably coincide. Second, different mechanisms may be active in different patients. Frequently occurring premature atrial complexes or atrial tachycardia (triggers) are important for paroxysmal atrial fibrillation; despite absence of structural heart disease (substrate) atrial fibrillation is repeatedly induced. Eventually, as a result of remodeling, a vulnerable substrate may develop, facilitating permanent atrial fibrillation. Another mode of induction occurs in the patient with structural heart disease (vulnerable electrical environment or substrate) in whom a single premature atrial complex may suffice. In this case, the substrate is relatively important for arrhythmia persistence. Conversely, many patients with structural heart disease never develop atrial fibrillation, either due to absence of triggers or unfavourable modulating factors, or due to yet unknown “protective” mechanisms. These possible scenarios illustrate that different chains (or pathophysiological processes) are possible. Figure 1 illustrates the interaction between the aforementioned factors, using the concept of the triangle of arrhythmia. Elements of atrial remodeling are initially considered to be modulating factors and are shown accordingly.
Eventually, however, these elements can acquire the status of substrate, which exemplifies the intractability of the arrhythmia. Yet, the determinants involved in the pathophysiology of atrial fibrillation should first be identified before an actual integrated concept can be made. Both fundamental research on the level of the atria (with electrophysiological, molecular biological, and histological techniques) and the critical evaluation of the outcome of current arrhythmia management (disclosing clinical factors of failure) are mandatory to reveal the determinants of arrhythmia intractability and to improve our understanding of the arrhythmia.

**Aims of the thesis**

The first aim was to investigate electrophysiological, neurohormonal, and autonomic nervous changes associated with human atrial fibrillation (Parts A & B). Appendices 1 and 2 deal with such consequences of the arrhythmia on the level of the atria, or more specifically, atrial remodeling. On a systemic level, appendices 3 and 4 illustrate neurohumoral and autonomic nervous system responses. The second aim was to illustrate these pathophysiological processes with respect to arrhythmia management in the setting of heart failure and atrial arrhythmia surgery (Part C). Appendices 5, 6, and 7 focus on the common intersection of atrial fibrillation and heart failure. Clinical course is studied in patients with both atrial fibrillation and heart failure. Finally, in appendices 8 and 9, the feasibility of surgery for atrial fibrillation after failure of conventional treatment is described.
Introduction

Basic and clinical aspects of atrial fibrillation

Atrial electrophysiological aspects
Atrial fibrillation implies absence of normal regular sinus rhythm and a random, chaotic electrical activation of the atria with a high frequency (350-600/min). The normal P-wave is absent on the surface electrocardiogram and the baseline consists of an irregular wave pattern, or “f-waves” (fibrillation waves). In the absence of total AV-block, the resulting ventricular response is totally irregular. The mechanism underlying the perpetuation of atrial fibrillation is multiple wavelet reentry. This concept was hypothesized by Moe in 1959, and subsequently supported by atrial “mapping” studies (Allessie 1985, Cox 1991, Konings 1994). The reentry circuit in atrial fibrillation is of the “leading circle” type, implying a functionally determined circuit, in contrast to e.g. common atrial flutter where it is anatomically determined. The center of such a functionally determined circuit is invaded by multiple centripetal wavelets, that collide and extinguish, resulting in an area of non-excitability (refractoriness). The circulating impulse travels across the myocardium along the shortest possible route, reexciting tissue as soon as it recovers from refractoriness. The distance travelled by a wavelet is determined by the refractory period and the conduction velocity: the wavelength equals conduction velocity times refractory period. This implies that, for atrial fibrillation to continue, the wavelength should “fit” in the atria. In dogs, the critical length is estimated to be about eight centimeters (Rensma 1988). In addition, a critical number of wavelets is necessary for atrial fibrillation to continue. In man, at least three coexistent wavelets seem required. To further illustrate the complexity of the electrophysiology of atrial fibrillation, as many as three types of temporal-spatial patterns of atrial fibrillation were identified in high-density atrial mapping studies in humans (Konings 1994). Inherent to the above considerations, certain conditions promote the induction and perpetuation of atrial fibrillation; a short refractory period, dispersion of refractoriness, depressed conduction velocity, or non-uniformity in conduction all promote atrial fibrillation. These electrophysiological conditions are frequently found in diseased or enlarged atria.

Recently, it was discovered that focal and rapidly firing premature atrial impulses (often originating from one of the pulmonary veins) trigger atrial
fibrillation. Once atrial fibrillation is induced, electrical remodeling will reinforce the perpetuation of the arrhythmia and facilitate reinduction. Removal of these foci with radio frequency (RF) ablation appears to be curative in the sense that it prevents induction of atrial fibrillation by removal of a triggering mechanism. (Haissaguerre 1998, Haissaguerre 2000). It illustrates that induction and perpetuation of the arrhythmia may be mediated through different mechanisms.

Apart from atrial fibrillation due to preexisting arrhythmogenic conditions, the arrhythmia itself produces atrial electrophysiological changes, thereby domesticating itself; "atrial fibrillation begets atrial fibrillation". In experiments conducted in goats, it was found that atrial refractoriness shortens within 24-48 hours of atrial fibrillation, without affecting conduction velocity (Wijffels 1995). Furthermore, the normal progressive shortening of atrial refractoriness at fast heart rates became absent or was even inverted. This process was named atrial electrical remodeling. Later experiments have suggested that electrical remodeling occurs in humans as well (Franz 1997, Pandozi 1998, Yu 1998). In the experiments by Allessie’s group, complete recovery from electrical remodeling was observed (within 1 week), suggesting reversibility of the process. Other animal studies show comparable results (Garratt 1999). The time course of reversal in “naturally” occurring atrial fibrillation in man appears to be within the same magnitude (within 1 week), but it is unclear whether the recovery is complete (Tanabe 1999, Yu 1999, Hobbs 2000). Heterogeneity in refractoriness (or nonuniform electrical remodeling) as a consequence of atrial tachycardia further enhances vulnerability to atrial fibrillation in a dog model (Fareh 1998). This would be another important factor enhancing intractability of atrial fibrillation. The clinical importance of electrical remodeling on top of chronic, structural heart disease remains to be determined.

The ionic or cellular mechanisms underlying the above mentioned electrical changes of the atria have gained widespread interest. In a study by Wijffels et al. it was concluded that autonomic modulation, ischemia, hemodynamic loading of the atria, and atrial natriuretic peptide administration do not mediate electrical remodeling (Wijffels 1997). Evidence points in a different direction, namely abnormal calcium handling by the atrial myocyte (De Pauw 1996, Van Wagoner 1997a, Yue 1997, Brundel 1999a, Van Gelder 1999a, Ausma 2000a).
Consequently, it was argued that a calcium-entry blocking agent might attenuate electrical remodeling, and improve the restoration and subsequent maintenance of sinus rhythm. Indeed, the use of verapamil seems to slow down or attenuate early electrical remodeling (Daoud 1997, Tieleman 1997, Lee 2000), while digoxin delays the recovery from electrical remodeling (Tieleman 1999). Retrospective data from our institute point to an improved arrhythmia outcome when intracellular calcium lowering drugs (initiated during atrial fibrillation) are continued after cardioversion (Tieleman 1998). Adding to this concept, it was recently shown in a prospective randomized study that verapamil added to a class 1c antiarrhythmic drug reduced both acute and subacute (within first week) arrhythmia recurrences (De Simone 1999). Whether calcium-entry blocking agents are truly useful in this respect will have to be confirmed by other randomized trials such as the “VERDICT-NHS” protocol, sponsored by the Netherlands Heart Foundation. In this Dutch study, patients with persistent atrial fibrillation will start with either verapamil or digoxin as rate control drug, and continue to use it during serial cardioversion therapy. The primary end-point of the study is subsequent maintenance of sinus rhythm. It is hypothesized that verapamil will improve arrhythmia outcome compared to digoxin.

**Atrial structural and functional aspects**

Paroxysmal atrial fibrillation in relatively young patients is frequently unassociated with cardiovascular disease. By contrast, persistent atrial fibrillation usually does not come alone; heart disease preceding persistent atrial fibrillation is the rule. An inherent dilemma in this respect is to distinguish which functional and structural atrial changes are “primary” and which are “secondary” to atrial fibrillation (Gallagher 1997b).

On the one hand, structural heart disease has definite influence on atrial structure and function. Rheumatic heart disease is associated with atrial fibrosis causing conduction delay. Valvular heart disease, congenital heart disease, and left ventricular dysfunction produce hemodynamic effects thereby loading and stretching the atria. This in turn affects electrophysiology (conduction, refractoriness). Indeed, deterioration in echocardiographically assessed diastolic parameters (indicative of progressive loss of atrial function) predicted the onset
of atrial fibrillation in patients with chronic heart failure (Pozzoli 1998). Heart failure may also promote atrial fibrillation by producing interstitial atrial fibrosis which affects conduction and refractoriness (Li 1999). Systemic hypertension itself does not impose a load on the left atrium, but once ventricular hypertrophy has developed diastolic dysfunction is likely, loading the left atrium. Ischemic heart disease is presumably associated with atrial fibrillation in the same fashion; diastolic ventricular dysfunction resulting from impaired relaxation secondary to ischemia loads the left atrium. Hyperthyroidism is also known to promote atrial fibrillation; in this instance by affecting cellular metabolism, thus probably changing electrophysiology. Other etiologies include pulmonary embolism, infections, cardiac surgery, or alcohol intoxication, but these will not be addressed in detail. Table 2 summarizes the most common cardiac and non-cardiac etiologies (or predisposing conditions) of atrial fibrillation.

On the other hand, atrial fibrillation produces functional and structural atrial responses. Although the chaotic atrial contraction pattern during atrial fibrillation depresses atrial function, it is not the only determinant. Atrial contractility also becomes impaired due to metabolic derangement (atrial stunning, or more correctly, hibernation (Van Gelder 1999b)), which becomes clear after cardioversion of persistent atrial arrhythmia (Jordaens 1993, Manning 1994). The longer the arrhythmia has lasted, the more prolonged and incomplete the recovery of atrial contractile function (as assessed by Doppler-echocardiography of transmitral flow). Eventually, after very long standing atrial fibrillation, atrial contractile function is lost permanently (even after cardioversion), accompanied by electrical and endocrinological “silence” (Seino 1991). At the same time, progressive atrial enlargement occurs during ongoing atrial fibrillation (Sanfilippo 1990). These findings suggest disrupted myocyte integrity. On a cellular level, it was found that persisting atrial fibrillation leads to cellular dedifferentiation and ultrastructural changes (Ausma 1997a, Ausma 1997b, Ausma 2000a). These adaptations resemble those found in chronic hibernating (“sleeping”) ventricular myocardium and are linked to a disturbed cellular calcium metabolism (Leistad 1996, Sun 1998). Although atrial size decreases again after cardioversion (Van Gelder 1991a, Gosselink 1993), it is unknown whether the (ultrastructural) cellular changes are
completely reversible. However, recent observations in a goat model of atrial fibrillation suggest partial reversibility (Ausma 2000b). Furthermore, irreversible damage such as atrophy (whether by apoptosis or necrosis) and interstitial fibrosis will also determine the extent of recovery from atrial remodeling (Li 1999). Recently, the occurrence of apoptotic death of atrial myocytes during atrial fibrillation was shown (Aime-Sempe 1999). Although the time course until “irreversibility” is unclear, four time domains in response to atrial fibrillation are proposed by Allessie (Allessie 1998). They comprise short-term (metabolic) changes, moderate-term changes (electrical remodeling), long-term changes (contractile remodeling), and very-long-term changes (anatomical remodeling). Of note, notwithstanding these distinctions, all changes presumably occur concomitantly as they are linked to a disturbed cellular calcium metabolism after the onset of the arrhythmia. Another important consideration is that initially “protective” atrial responses or adaptations may eventually have detrimental effects.

Apart from effects on the atrial level, the ventricle may also become depressed by the arrhythmia. In animal models, ventricular systolic and diastolic remodeling secondary to atrial tachycardia have been described (Spinale 1990). In man, after cardioversion of persistent atrial fibrillation, left ventricular ejection fraction slowly improves in the month thereafter (Van Gelder 1993). An increase in left ventricular function has also been observed after His bundle or AV-node ablation (Heinz 1992, Brignole 1994). These data indicate that atrial fibrillation causes some degree of left ventricular dysfunction or “tachycardiomyopathy” which is at least partial reversible. Although this effect may be secondary to high rate there is evidence that the irregularity of heart rate per se also depresses ventricular function (Daoud 1996, Clark 1997). In other words, tachycardiomyopathy may be inherent to atrial fibrillation. Nevertheless, lowering of high ventricular rate per se is important as it may improve ventricular function (Van den Berg 1993). On a structural level, studies on ventricular abnormalities secondary to atrial fibrillation were conducted in animal models with rapid atrial pacing, showing cellular dedifferentiation and alterations in collagen tissue structure (Spinale 1991a, Spinale 1991b).
Atrial ultrastructural cellular aspects

The genetic basis of atrial fibrillation is an unexplored area. Although the arrhythmia seems to occur in families, its expression is variable and the overlap with naturally occurring, age-related atrial fibrillation makes it difficult to identify familial cases. One typical example is a Spanish family with a genetic defect underlying atrial fibrillation (Brugada 1997). Nevertheless, the discovery of atrial tachycardia-induced electrical remodeling has led to numerous studies on ion channel activity (or current density), protein expression, and mRNA expression. Additionally, contractile remodeling of the atria in response to atrial tachycardia or fibrillation has put a focus on changes in cellular calcium handling.

Ultrastructural cellular changes as a consequence of atrial fibrillation

Rapid atrial tachycardia in dogs reduced \( I_{\text{Cal}} \) (depolarizing current during the plateau phase) and \( I_{\text{to}} \) (outward \( K^+ \)-current) densities without concomitant changes in kinetics and voltage dependence (Yue 1997). In subsequent experiments, the observed changes seemed to correspond with a reduced number of functional L-type \( Ca^{2+} \)-channels (transcriptional down-regulation) rather than an alteration in ion channel properties (Yue 1999). So far, no changes in density of \( I_{K1} \) (inward rectifier), \( I_{KR} \) and \( I_{KS} \) (rapid and slow delayed rectifier), \( I_{to2} \) (calcium dependent \( Cl^- \)-current), or T-type \( Ca^{2+} \)-channel were observed in this model. Besides changes in refractoriness, slowing of conduction velocity in atrial tachycardia occurs as well, albeit with delay (Gaspo 1997a). These alterations are paralleled by a progressive reduction of \( I_{Na} \) due to attenuated gene expression (Yue 1999).

Investigating (ultrastructural) cellular mechanisms of electrical remodeling in man is difficult because of uncontrolled variables such as age, underlying cardiac disease, and concomitant medication. Nevertheless, \( I_{\text{Cal}} \) density proved to be lower in patients undergoing cardiac surgery with atrial fibrillation as compared to sinus rhythm (Van Wagoner 1999). Furthermore, \( I_{to} \) and \( I_{Ksus} \) densities were depressed, accompanied by a lower mRNA expression of Kv1.5 which is encoding for the ultra rapid component of the delayed rectifier (Van Wagoner 1997b). In line with these data, we demonstrated a lower mRNA expression of the L-type \( Ca^{2+} \)-channel in patients with atrial fibrillation of a duration >6 months (Van Gelder 1999a). Comparable results were obtained by
Lai et al., who showed that atrial fibrillation with a long duration (>3 months) was associated with a reduced mRNA expression of the L-type Ca\(^{2+}\)-channel (Lai 1999a). In addition, this group observed an up-regulated mRNA expression of the \(I_{f(u)nny}\) channel (pacemaker current) in human atrial fibrillation (Lai 1999b). In patients with persistent atrial fibrillation scheduled for maze surgery we demonstrated depressed mRNA levels of genes encoding for \(I_{CaL}, I_{to}, I_{KAdh}\) (acetylcholine dependent potassium channel), and \(I_{KATP}\). mRNA expression of the Na\(^+\)-channel was also decreased, although to a moderate extent. No changes were found for \(I_{KR}\) and \(I_{KUR}\) (ultra rapid component of the delayed rectifier) (Brundel 1999b).

All these changes are in accordance with an important role of the L-type Ca\(^{2+}\)-channel in electrical remodeling after longstanding atrial fibrillation, but cannot sufficiently explain acute action potential shortening and impaired rate adaptation. Only recently, however, Bosch et al demonstrated increased \(I_{K1}\) and \(I_{KAdh}\) in patients with a relatively short duration of atrial fibrillation which would be in accordance with the acute electrophysiological changes (Bosch 1999). Pertaining to intracellular calcium handling, mRNA expression of SERCA (sarcoplasmatic reticulum Ca\(^{2+}\)-ATPase), phospholamban, and the Na\(^+\)/Ca\(^{2+}\)-exchanger appear to be unchanged in persistent (>6 months) atrial fibrillation (Van Gelder 1999a). In another set of patients, however, we did observe decreased mRNA and protein expression of SERCA (Brundel 1999a). Lai et al showed a reduced gene expression of SERCA as well (in patients with atrial fibrillation >3 months duration), but without changes in mRNA expression of phospholamban and the ryanodine receptor (Lai 1999a).

These data on cellular calcium handling and ion channel function in atrial fibrillation point to profound effects. Still, it is important to separate influences of the arrhythmia from underlying cardiac disease, which may not be always as easy. Although it seems clear that atrial fibrillation produces ultrastructural atrial changes, the signaling pathways remain to be clarified.

**Autonomic nervous system and neurohormonal aspects**

Both sympathetic and parasympathetic (or vagal) nerve fibers supply the atria. The right hand part of the autonomic nervous system subserves the right atrium (and SA-node), whereas the left hand part subserves the left atrium (and AV-
Right-left differences in atrial autonomic innervation are therefore intrinsic. Furthermore, the distribution of vagal innervation of the atria is nonuniform (Alessi 1958). The afferent cardiac nerve fibers conduct impulses from the heart to the brain stem, where integration with other signals elicit cardiopulmonary reflex mechanisms. The efferent cardiac nerve fibers release neurotransmitters enacting on the myocardial cells.

**Influences of the autonomic nervous system on the arrhythmia**

Sympathetic stimulation moderately decreases the refractory period, enhances automaticity, but hardly affects conduction velocity in the atria (Zipes 1974, Shimizu 1994). Vagal stimulation, on the other hand, markedly shortens atrial refractoriness (Zipes 1974, Prystowsky 1983, Shimizu 1994). Furthermore, automaticity will be suppressed. Again, conduction velocity is hardly altered, but anisotropic conduction and dispersion will become more pronounced. Both limbs of the autonomic nervous system thus heighten susceptibility to atrial arrhythmia. Moreover, sympathetic and vagal activity do not exclude one another; both may be active at the same time. In fact, vagal effects are more pronounced in the presence of a high sympathetic tone and vice versa ("accentuated antagonism") (Levy 1971). When a premature atrial beat "hits" the atria at a point in time when autonomic tone has created favourable conditions for atrial arrhythmia to occur (in particular shortened refractoriness), both initiation and perpetuation of atrial fibrillation are facilitated. In addition to the above, vagal stimulation produces a marked variability in atrial refractoriness, which also facilitates atrial fibrillation (Liu 1997). To illustrate the importance of autonomic influences, artificially mimicked vagal stimulation of the atria with acetylcholine or methylcholine is known to strongly facilitate atrial fibrillation and is therefore used in experimental settings.

Onset of (paroxysmal) atrial fibrillation in a vagal setting, or vagally mediated (paroxysmal) atrial fibrillation, is a concept first described by Coumel in 1978. According to his description, atrial fibrillation typically occurs at night or at rest, and is preceded by bradycardia with frequent atrial premature beats. During the course of the disease, this pattern may disappear (personal observation). Conversely, sympathetically mediated onset of atrial fibrillation typically occurs during exercise or emotional stress (Sopher 1997). Of note, the conditions which elicit sympathetically mediated onset of atrial fibrillation...
Introduction

are similar to those which elicit ischemia in patients with coronary artery disease. This is illustrated by a case-control study in a large group of patients undergoing exercise testing; of the patients in whom atrial fibrillation was induced 26% suffered from ischemic heart disease (Van den Berg 1994). Apart from the typical clinical examples, however, the incidence of purely neurally mediated atrial fibrillation is unknown. Nevertheless, evidence is accumulating that alterations in autonomic tone (as assessed by heart rate variability analysis) may precede paroxysms of atrial fibrillation (Hnatkova 1998, Sopher 1998). Vagal conditions at night appear to be of particular importance. However, in the above mentioned “CRAFT” trials, single patients did not show one consequent mode of onset. Clearly, this inconsistency hampers the translation to a clinical strategy. Therefore, controlled studies are needed to identify optimal treatment of patients with paroxysms of atrial fibrillation preceded by alterations in autonomic tone (Andresen 1998).

The substrate for the susceptibility to atrial fibrillation in the setting of autonomic changes is not evident. Nonuniformity in autonomic innervation facilitates atrial fibrillation in animal experiments (Olgin 1998). It is conceivable that atrial myocarditis or fibrosis may produce nonuniformity in autonomic innervation (or nervous damage), thus facilitating atrial fibrillation later in life (Lie 1997). Other possibilities include imbalance between vagal tone and sympathetic tone or anatomical aberrations such as pronounced right-left differences of autonomic pathways.

Limited data are available on circulating neurohormones and/or catecholamines in relation to predisposition to atrial fibrillation. Examples of neurohormones with cardiac effects are renin, angiotensin-II, atrial natriuretic peptide, brain natriuretic peptide, endothelin, dopamine, epinephrine, and norepinephrine. Theoretically, premature atrial beats may be induced by these catecholamines, favouring atrial fibrillation when a substrate is present. Although these neurohormones play an important role in the pathophysiology of (congestive) heart failure, it is unclear which hormonal profile predicts the onset of atrial fibrillation. Recently, however, higher N-terminal atrial natriuretic peptide levels in patients with advanced heart failure demonstrated to be predictive for developing atrial fibrillation (Crijns 2000). In line with these findings, elevated plasma atrial natriuretic peptide also seems to have prognostic value.
Influences of the arrhythmia on the autonomic nervous system

In general, tachycardia often cause a blood pressure fall at onset, eliciting compensatory sympathetic activation and vagal withdrawal (Waxman 1995). These effects are mainly mediated through stimulation of baro- and mechanoreceptors. Of interest, autonomic modulation (for instance carotid sinus pressure) may terminate atrial tachycardia, but in atrial fibrillation it is ineffective due to the multiple reentry character of the arrhythmia. More specifically, autonomic effects in atrial fibrillation are hard to measure with heart rate variability techniques, given the irregularity of ventricular rate. Nevertheless, heart rate variability during atrial fibrillation reflects to some extent vagal modulation of AV-node function (Van den Berg 1997). However, comparing these data to sinus rhythm (SA-node function) is as yet impossible. Using heart rate variability analysis, rebound vagal activity was observed after termination of 24 hours of rapid atrial pacing (mimicking atrial fibrillation) in a goat model (Blaauw 1999). In line with general observations on tachycardia, these data suggest attenuation of vagal activity during atrial fibrillation. Even more recently, it was demonstrated that atrial fibrillation is associated with a nonuniform increase in atrial sympathetic innervation, especially of the right atrium (Jayachandran 2000). These changes parallel the disparate effects of atrial fibrillation on atrial electrophysiology. The relevance of these findings (suggesting autonomic remodeling) in relation to the intractability of atrial fibrillation remains to be analyzed.

In contrast to predisposition to atrial fibrillation, more data are available on neurohormonal effects as a consequence of atrial fibrillation. Circulating atrial natriuretic peptide rises after the onset of atrial fibrillation (Roy 1987), and it is responsible for the often reported symptom of polyuria during or shortly after a paroxysm. A complete “family” of natriuretic peptides has been identified (including brain natriuretic peptide, and C-type natriuretic peptide), but the effects are best described for atrial natriuretic peptide. The stimulus for its production is atrial stretch. The hormone exercises fluid balance regulation on the level of the kidney (natriuresis) and hemodynamic correction through...
vasodilatation (mediated by vagal action), whereas its cardiac effects involve decreased cellular calcium loading, action potential shortening, and slowing of phase 4 depolarization (thus prolonging myocyte relaxation) (Clemo 1996). The cardiac effects of atrial natriuretic peptide might therefore be summarized as “protective” when cellular calcium overload is concerned. It should be noted that besides atrial tachycardia, stretch secondary to heart failure and cardiovascular medication influence atrial natriuretic peptide levels as well. A new approach to investigate neurohormonal changes is molecular biology, enabling the investigation of gene and/or protein expression. With these techniques, it was found that atrial mRNA expression of both atrial natriuretic peptide and brain natriuretic peptide correlate with atrial pressure (Doyama 1998). Still, the molecular mechanism on a (ultra)cellular level remains to be clarified, specifically how atrial fibrillation triggers the above mentioned neurohormonal release.

Few data exist on other neurohormonal systems. So far, in the setting of atrial tachycardia, the acute effects do not appear to involve general activation of the renin-angiotensin-aldosterone system (Kojima 1988, Nicklas 1989). Possibly, the elevated atrial natriuretic peptide depresses aldosterone secretion. Recently, however, blocking the angiotensin II type 1 receptor (AT₁-R) proved to prevent electrical remodeling, suggesting involvement of a local tissue renin-angiotensin-aldosterone mechanism in atrial fibrillation (Nakashima 2000). Only very recently, it was shown that atrial fibrillation is associated with down-regulation of atrial AT₁-R and up-regulation of AT₂-R proteins (Goette 2000). How these findings would translate to a general role of the renin-angiotensin-aldosterone system in remodeling in atrial fibrillation remains unclear. As observed in a clinical study, renin-angiotensin-aldosterone system inhibition with an ACE-inhibitor might have favourable effects on arrhythmia outcome (Van den Berg 1995). It can be hypothesized that ACE-inhibition or AT₁-R blockade may modulate arrhythmia intractability through inhibition of both local tissue and systemic renin-angiotensin-aldosterone systems. Although it has been suggested that other vasoactive compounds such as vasopressin, prostaglandin E2, endothelin, and cyclic-AMP are involved in the pathophysiology of atrial fibrillation (Imanishi 1990, Li 1995, Theodorakis 1996), this remains to be fully clarified. Of note, in case of development of tachycardia-induced cardiomyopathy (associated with heart failure), other
neurohormones besides the natriuretic peptides will become elevated (Shinbane 1997). Importantly, advanced neurohormonal activation may contribute to atrial remodeling and disease progression to significant extent.

Another aspect of the autonomic nervous system relates to symptoms in atrial fibrillation. So far, only a few studies have systematically addressed complaints and quality of life in patients with atrial fibrillation (Jenkins 1996, Jung 1998). Moreover, most available studies pertain to highly symptomatic patients who underwent AV-node ablation for “drug refractory” atrial fibrillation (Brignole 1994, Brignole 1998). Conversely, data on the “average” symptomatic patient are lacking. At present, large clinical trials randomizing to different treatments for atrial fibrillation (AFFIRM, PIAF, RACE) have incorporated quality of life measurement in their design (AFFIRM Investigators 1997, Hohnloser 1997, Verdoes 2000). In addition, it is conceivable that ones personality plays a role in this connection. In the presence of a “neurotic” personality, the perception of the effect of the arrhythmia may be amplified. In turn, such a perception could promote unfavourable autonomic modulation, thus enhancing arrhythmia susceptibility. There is some indication that an abnormal autonomic response, arrhythmia susceptibility, and impaired quality of life correlate, though this pertains to selected patients with orthostatically induced supraventricular arrhythmias (Braune 1999).

**Heart failure**

Atrial fibrillation and heart failure are associated disorders, especially in elderly patients, owing to common risk factors (Wolf 1996). On the one hand, the arrhythmia emerges in the presence of (progressing) heart failure. A poor ventricle loads the atria and induces stretch. In turn, this may result in action potential prolongation and stretch-activated after-depolarizations of the atrium, or, “mechano-electric feedback” (Kamkin 2000). At the same time, chronic stretch may eventually result in atrial enlargement (Solti 1989). Structural changes like interstitial fibrosis may also contribute to an arrhythmogenic environment (Li 1999). In addition, elevated neurohormone levels in response to heart failure may initiate atrial after-depolarizations and hereby trigger atrial fibrillation. In accordance with these considerations, many of the patients in heart failure trials have atrial fibrillation. Table 3 shows a number of
Table 3. Prevalence of atrial fibrillation in studies on heart failure

<table>
<thead>
<tr>
<th>Predominant NYHA class</th>
<th>Mean LVEF</th>
<th>Prevalence AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD-prevention 1992</td>
<td>I</td>
<td>0.28</td>
</tr>
<tr>
<td>SOLVD-treatment 1991</td>
<td>II-III</td>
<td>0.25</td>
</tr>
<tr>
<td>CHF-STAT 1995</td>
<td>II-III</td>
<td>n.a.</td>
</tr>
<tr>
<td>MERIT-HF 1999</td>
<td>II-III</td>
<td>0.28</td>
</tr>
<tr>
<td>Middlekauff 1991</td>
<td>III-IV</td>
<td>0.19</td>
</tr>
<tr>
<td>Stevenson 1996</td>
<td>III-IV</td>
<td>0.23</td>
</tr>
<tr>
<td>GESICA 1994</td>
<td>III-IV</td>
<td>0.20</td>
</tr>
<tr>
<td>CONSENSUS 1987</td>
<td>IV</td>
<td>n.a.</td>
</tr>
</tbody>
</table>


prominent trials on heart failure. The prevalence of atrial fibrillation increases with more advanced heart failure (as assessed by NYHA class). On the other hand, as discussed earlier, the arrhythmia per se may mediate in the deterioration of cardiac performance. Table 4 summarizes the underlying mechanisms. In line with the latter concepts, atrial fibrillation independently increases the risk for subsequent heart failure (Krahn 1995). Thus, the relation between atrial fibrillation and heart failure appears reciprocal; one aggravating the other. Finally, the influence of (progressing) underlying heart disease should be considered. In this connection, it seems reasonable to assume a deleterious effect on both heart failure and atrial fibrillation.

The impact of atrial fibrillation on survival in the setting of heart failure is the subject of controversy. Atrial fibrillation and heart failure both limit prognosis, but the impact of the arrhythmia superimposed on heart failure is not completely clear. In the past, it was common practice to treat atrial fibrillation with class I antiarrhythmic drugs, including patients with heart failure. Only later it became clear that survival was reduced when such antiarrhythmics were used in patients with heart failure (CAST Investigators 1989, Coplen 1990). More specifically, when patients with atrial fibrillation
were treated with class I antiarrhythmic drugs in the presence of heart failure, mortality was markedly increased as compared to mortality in patients without heart failure (Flaker 1992). Hence, the earlier reported negative impact of atrial fibrillation on survival in patients with heart failure might be the result of adverse effects of class I antiarrhythmics and not due to the arrhythmia itself (Middlekauff 1991, Stevenson 1995). Conversely, a class III antiarrhythmic drug such as amiodarone is of value in the setting of atrial fibrillation and heart failure. The CHF-STAT trial showed that patients converting to sinus rhythm on amiodarone have a lower mortality than nonconverters (Deedwania 1998). In addition, the drug is potent in maintaining sinus rhythm after cardioversion in patients with a compromised left ventricular function (Gosselink 1992).

Another essential therapy for improving cardiac condition is ACE-inhibition. In the first place, an ACE-inhibitor may prevent atrial fibrillation in the presence of heart failure (Pedersen 1999). Secondly, when ACE-inhibition is initiated before cardioversion, subsequent restoration and maintenance of sinus rhythm may improve (Van den Berg 1995). Thirdly, ACE-inhibition may reduce mortality in the setting of atrial fibrillation and heart failure (Dries 1998), comparable to its effects in patients with heart failure in sinus rhythm (SOLVD, SAVE, and other trials). At present, the arrhythmia appears not to have a significant independent impact on survival when therapy including ACE-inhibition and amiodarone is instituted (Stevenson 1996, Crijns 2000).

Although the value of cardiac unloading drugs seems evident, this is less well defined for serial cardioversion therapy. Essentially patients with true

| Table 4. Mechanisms underlying deterioration of cardiac performance in atrial fibrillation |
|---------------------------------|--------------------------------------------------------------------------------------------|
| 1. Loss of organized atrial contraction |                                                                                           |
| 2. High ventricular rate | - decreased diastolic filling time  
- decreased stroke volume |
| 3. Irregularity of ventricular rate |                                                                                           |
| 4. Ventricular tachycardiomyopathy |                                                                                           |
| 5. Progressive neurohormonal derangement |                                                                                           |
| 6. Progressive underlying cardiac disease |                                                                                           |
tachycardiomyopathy benefit from restoration of sinus rhythm or adequate lowering of ventricular rate alone. Yet, it can be difficult to recognize tachycardiomyopathy in the setting of atrial fibrillation and heart failure. As an adjunct to routine diagnostics, low-dose dobutamine stress echocardiography may help to identify patients benefitting from restoration of sinus rhythm with recovery of left ventricular function (Paelinck 1999). Still, it is unclear whether a cardioversion strategy is of real long-term use for these and other patients with atrial fibrillation and heart failure. Can serial cardioversion prevent the recurrence of either heart failure or atrial fibrillation, and, can it improve survival? Therefore, we need to focus on patients with atrial fibrillation and heart failure who undergo serial cardioversion. Anticipating on the results, such a strategy might be of limited value as it is indicated that long-term maintenance of sinus rhythm is only possible in a minority of patients (Van Gelder 1996). Obviously, alternative treatment strategies are pharmacological rate-control therapy or AV-nodal ablation. The latter seems to be useful in a highly symptomatic patient (Brignole 1998), but is not suited for every patient with atrial fibrillation and heart failure. Thus, the optimal arrhythmia therapy in the presence of heart failure is still undetermined.

In heart failure, elevated plasma and tissue neurohormones such as angiotensin-II mediate in the pathophysiology of disease progression. Increased neurohormonal levels bring about ventricular hypertrophy, cellular dedifferentiation, and interstitial fibrosis which in turn causes progression of heart failure and ventricular arrhythmia (Cohn 2000). As stated in the previous section, atrial fibrillation is also associated with neurohormonal activation, although atrial natriuretic peptide is the main actor in this setting. Comparable to heart failure, the altered neurohormonal (and autonomic) status in atrial fibrillation might procure cellular adaptations in the ventricles. Thus, the occurrence of heart failure secondary to atrial fibrillation might be mediated through neurohormonal effects of the arrhythmia on a ventricular level. Until now, specific data on the neurohormonal profile of patients with atrial fibrillation and heart failure are lacking. Such data are of interest as they may indicate the importance of atrial fibrillation in the setting of heart failure. Atrial natriuretic peptide is of special interest since this neurohormone is mainly produced in the atria and exercises “protective” properties acting as a diuretic
and as an opponent of the renin-angiotensin system. During the time course of atrial fibrillation, however, atrial natriuretic peptide production progressively declines to a point where levels become undetectably low (Seino 1991, Van den Berg 1998). One might argue that loss of such a protective mechanism contributes to heart failure. Possibly, patients developing heart failure during atrial fibrillation can be identified by declining atrial natriuretic peptide levels. Nevertheless, the pathophysiology of atrial natriuretic peptide (and other natriuretic peptides) in general needs to be investigated to greater extent in patients with atrial fibrillation either with or without accompanying heart failure.

**Therapeutic aspects**

At present, antiarrhythmic drugs are still the cornerstone of therapy for atrial fibrillation (Van Gelder 1998), either by aiming at sinus rhythm (usually a Vaughan Williams class I or III drug) or by aiming at adequate ventricular rate control (usually a Vaughan Williams class II or IV drug, or digoxin).

**Cardioversion therapy for atrial fibrillation**

Restoring sinus rhythm with external electrical cardioversion is considered standard therapy for atrial fibrillation, and is widely practiced. Terminating human cardiac arrhythmias with electricity (R-wave synchronized capacitor discharge) was introduced by Lown in 1962. Only in patients with short-term (<24 hours) atrial fibrillation, pharmacological cardioversion with an intravenous class Ic antiarrhythmic drug is worth trying; it effectively restores sinus rhythm in >90% of the patients (Crijns 1988, Van Gelder 1999b). Currently, it is still a matter of debate whether sinus rhythm should be restored in every patient with atrial fibrillation. However, patients with atrial fibrillation of a duration less than 36 months, age below 57 years, left atrial size <60 mm (long axis view), and NYHA class I or II are generally considered suitable candidates for cardioversion therapy or at least one attempt (Van Gelder 1996, Van Gelder 1997). In general, all antiarrhythmic drugs for prophylaxis of atrial fibrillation are equal but they are only moderately effective (Crijns 1991). Only amiodarone (possessing class I,II and IV properties on top of a class III effect) is more effective (Roy 2000), but its non-cardiac adverse effects and abnormal pharmacokinetics pose important disadvantages. When applying serial
Introduction

electrical cardioversion combined with serial antiarrhythmic drug therapy (including amiodarone), only 27% of the patients maintain sinus rhythm after 4 years of therapy (Van Gelder 1996). It should be stressed that during this strategy, antiarrhythmic drugs were not only discontinued due to inefficacy (recurrent atrial fibrillation despite adequate doses), but also because of cardiac and non-cardiac side effects.

The currently used serial electrical cardioversion strategy is probably not optimal. Preparatory anticoagulative therapy and waiting lists hamper its potential effectiveness. Early cardioversion of atrial fibrillation (“as soon as possible”), may increase eventual efficacy by early interruption of processes of atrial remodeling. Indeed, the “MEDCAR” study from our institute indicates that, in case of an arrhythmia recurrence, prompt re-cardioversion facilitates the efficacy of antiarrhythmic drug use in restoring sinus rhythm (Tieleman 2000). In addition, drugs preventing or delaying atrial remodeling (for instance, a calcium entry blocker) could enhance the success-rate of cardioversion therapy. The “VERDICT-NHS” study is a prospective clinical trial investigating these issues; patients will receive either verapamil or digoxin >4 weeks prior to cardioversion and will be re-cardioverted either immediately (<24 hours) or scheduled (<4 weeks) in case of an arrhythmia recurrence. The primary endpoint is permanent (accepted) atrial fibrillation after 1.5 years of follow-up.

On the one hand, rhythm-control may lower the incidence of heart failure, thromboembolism, bleeding, and improve quality of life, but is rather ineffective and time consuming. In addition, patients remain at risk for thromboembolism at the very moment the arrhythmia recurs. On the other hand, rate-control therapy also may lower the incidence of heart failure, but it necessitates continued anticoagulation and quality of life might be reduced. Still, it is void of the dangers of (prophylactic) antiarrhythmic drug therapy and usually easy to carry out. Consequently, striving for sinus rhythm may not be the right goal in the treatment of atrial fibrillation. Several large scale clinical studies (AFFIRM, PIAF, RACE), comparing “rhythm-control versus rate-control” with a focus on survival, complications, and quality of life, are currently in progress (AFFIRM Investigators 1997, Hohnloser 1997, Verdoes 2000). Preliminary results of the PIAF study indicate that both strategies yield similar improvement in symptoms and quality of life (after 1 year of treatment) but
exercise tolerance is better in the group of patients with restored sinus rhythm (Hohnloser 1999). It should be emphasized, however, that the aforementioned projects (AFFIRM, PIAF, RACE) utilize “non-optimal” serial cardioversion.

Unconventional therapy for atrial fibrillation
Acceptance of the arrhythmia is the first option after failure of serial antiarrhythmic drug and cardioversion treatment (rhythm-control). Still, in some patients conventional rate-control therapy fails or is not feasible due to persisting symptoms despite optimal rate-control management (including adequate rate-response to exercise) or rate-control drug intolerance. Therefore, new, unconventional treatment strategies mainly aiming at symptom reduction have been developed.

1. Permanent cardiac pacing (with or without AV-node ablation)
Catheter-guided RF-ablation of the AV-node with subsequent permanent ventricular pacing is a relatively new and promising concept. A recent meta-analysis of 21 studies on AV-node ablation and permanent pacing indicates improvement for a broad range of clinical outcomes (Wood 2000). Most data, however, pertain to selected, highly symptomatic patients (Fitzpatrick 1996, Brignole 1997, Marshall 1999). These studies indicate (moderate) improvement of quality of life and symptom reduction. Patients with left ventricular dysfunction are of particular interest, since small-size studies have indicated improvement of left ventricular function after AV-node ablation and permanent pacing (Rodriguez 1993). Other studies, however, could not demonstrate such an effect (Brignole 1998). So, it is not proven that AV-node ablation is advantageous in every patient with heart failure and a large scale investigation seems mandatory (Saxon 1997). Preventive single or dual site atrial pacing is another, relatively new, promising concept (Murgatroyd 1994). Such a strategy may be worth trying in patients who are candidates for AV-node ablation. If sinus rhythm is maintained, AV-node ablation can be avoided whereas it can still be executed in case of failure of pacing. The rationale is that permanent atrial pacing will reduce premature atrial beats, conduction delay, abrupt changes in heart rate, or dispersion in refractoriness (related to bradycardia), hereby attenuating the induction of atrial fibrillation (Ramdat Misier 1999). The initial trials determining optimal pacing mode are promising, particularly
in patients with a tendency towards bradycardia or sick-sinus syndrome (Ricci 1996). At present, a trial (AF-therapy project) comparing different algorithms of preventive pacing is in progress.

2. Catheter-guided radiofrequency ablation of the initiating focus
Catheter-guided RF-ablation of a single site of premature atrial complexes or fast atrial tachycardia may prevent the onset of atrial fibrillation in selected patients (Haissaguerre 1998, Haissaguerre 2000). The region of the pulmonary veins in the left atrium and the crista terminalis in the right atrium are of special interest. Particularly in patients with lone atrial fibrillation these locations are associated with premature atrial complexes or fast atrial tachycardia. Although selected series report high success rates of catheter-guided RF-ablation, this has not been obtained in other centers. It appears that the technique to eliminate foci in the pulmonary veins must be improved.

3. Implantable atrial defibrillator (or atrioverter)
Another recent development is the implantable atrial defibrillator. Initial experience with this “atrioverter” device is very promising (Wellens 1998, Timmermans 2000). It should be noted that this treatment is not primarily preventive; it only operates once atrial fibrillation occurs. The duration of episodes of atrial fibrillation can thus be shortened. The prevention of electrical remodeling would be an additional effect, thereby reducing the susceptibility to atrial fibrillation. Pain perception of the DC-shock may limit general use; even at low energy levels (below atrial fibrillation threshold) shock delivery is rather discomfoting.

4. Atrial arrhythmia surgery
Another resort for pharmacologically refractory atrial fibrillation is atrial arrhythmia surgery. Table 5 summarizes a number of studies on atrial arrhythmia surgery. Compartment surgery, left atrial isolation, and corridor surgery are moderately effective techniques (64-70% sinus rhythm after follow-up) that do not restore normal sinus rhythm in both atria (Graffigna 1992, Shyu 1994, Van Hemel 1994). These techniques create a pathway from sinus node to AV-node, either with or without inclusion of the right atrium, reducing atrial mass and hence atrial fibrillation susceptibility. Consequently, bi-atrial
<table>
<thead>
<tr>
<th>Year</th>
<th>Surgery</th>
<th>Combined*</th>
<th>N</th>
<th>F/U (months)</th>
<th>Sinus rhythm</th>
<th>SSS+PM</th>
<th>Complications</th>
<th>Low A-wave MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graffigna 1992</td>
<td>Left atrial isolation (MVR/AVR)</td>
<td>Yes</td>
<td>100</td>
<td>2-28</td>
<td>70%</td>
<td>3%</td>
<td>3 deaths (late)</td>
<td>not applicable</td>
</tr>
<tr>
<td>McCarthy 1993</td>
<td>Maze I</td>
<td>Mixed</td>
<td>14</td>
<td>3</td>
<td>100% +AAD</td>
<td>14% (preop-SSS)</td>
<td>1 death</td>
<td>0% (after MRI or TEE)</td>
</tr>
<tr>
<td>Van Hemel 1994</td>
<td>Corridor</td>
<td>No</td>
<td>36</td>
<td>41±16</td>
<td>69% -AAD</td>
<td>16%</td>
<td>9 re-surgery for AF</td>
<td>not applicable</td>
</tr>
<tr>
<td>Shyu 1994</td>
<td>Compartment</td>
<td>Yes (MVR+other)</td>
<td>22</td>
<td>6</td>
<td>64%</td>
<td>0%</td>
<td>none</td>
<td>7%</td>
</tr>
<tr>
<td>Kosakai 1994</td>
<td>Maze II-III+cryo (MVR only)</td>
<td>Yes</td>
<td>62</td>
<td>6-25</td>
<td>84%</td>
<td>3%</td>
<td>none</td>
<td>29%</td>
</tr>
<tr>
<td>Kosakai 1995</td>
<td>Maze II-III+cryo</td>
<td>Yes</td>
<td>101</td>
<td>12-37</td>
<td>82%</td>
<td>4%</td>
<td>2 deaths</td>
<td>27%</td>
</tr>
<tr>
<td>Gregori, Jr. 1995</td>
<td>Maze +cryo (MVR only)</td>
<td>Yes</td>
<td>20</td>
<td>6-15</td>
<td>90% -AAD</td>
<td>0%</td>
<td>none</td>
<td>10%</td>
</tr>
<tr>
<td>Cox 1995</td>
<td>Maze I-III</td>
<td>Mixed</td>
<td>111</td>
<td>3-81</td>
<td>99% +AAD</td>
<td>29% maze II</td>
<td>3 deaths</td>
<td>36% maze II 6% maze III</td>
</tr>
<tr>
<td>Kamata 1997</td>
<td>Maze III</td>
<td>Yes</td>
<td>104</td>
<td>12</td>
<td>73% +AAD</td>
<td>6%</td>
<td>4 deaths</td>
<td>not measured</td>
</tr>
<tr>
<td>Cox 1998</td>
<td>Maze III</td>
<td>Mixed</td>
<td>155</td>
<td>3-60</td>
<td>96% -AAD</td>
<td>0/111 without preop-SSS</td>
<td>?</td>
<td>9/155 (only 1/9 after TEE)</td>
</tr>
<tr>
<td>Jessurun 2000</td>
<td>Maze III</td>
<td>No</td>
<td>41</td>
<td>31±16</td>
<td>95% +AAD</td>
<td>5%</td>
<td>none</td>
<td>35%</td>
</tr>
<tr>
<td>Tuinenburg 2000</td>
<td>Mini-maze</td>
<td>Yes (MVR only)</td>
<td>13</td>
<td>12</td>
<td>82% +AAD</td>
<td>0%</td>
<td>1 death</td>
<td>absent in 1</td>
</tr>
</tbody>
</table>

* = atrial arrhythmia surgery combined with other cardiac surgery; yes, no, or mixed population.
AAD = antiarrhythmic drug, AF = atrial fibrillation, AVR = aortic valve replacement, F/U = follow-up, MRI = magnetic resonance imaging, MV = mitral valve, MVR = MV replacement, PM = pacemaker, SSS = sick sinus syndrome, TEE = transesophageal echocardiography.
function and AV-synchrony is not restored. The maze procedure, introduced in 1987 by Cox, consists of a labyrinth of atrial incisions (preventing reentry) and bilateral atrial appendage removal (reducing critical mass). After the procedure, sinus rhythm is propagated to both atria, by predetermined routes, imposed by the discrete incisions ("ablative sutures"). This procedure is rather extensive, with multiple incision lines in both atria, the interatrial septum, and around the pulmonary veins. Usually, local cryoablation is applied where the incisions approach the AV-ridge. The procedure has been applied to patients with and without structural heart disease, with long-term success rates of 73-96% in terms of maintenance of sinus rhythm (Gregori, Jr. 1995, Kosakai 1995, Kamata 1997, Cox 1998, J essurun 2000). However, the original maze procedure (maze I) was associated with postoperative sinus node dysfunction (Sundt 1997). The technique was therefore modified two times (maze II, maze III) to enlarge the “free” region of the sinus node. A second motive was better exposure of the left atrium to improve contractile function. Maze III is now the preferred technique; a blunted sinus node response is present in only 8% and left atrial contractile dysfunction in only 9% of the patients (Sundt 1997). More recently, several prominent thoracic surgeons have evaluated their personal experience with maze surgery over the past years. They all conclude that, in selected patients, it is a feasible alternative (Arcidi, Jr. 2000, Cox 2000, Kosakai 2000, McCarthy 2000, Schaff 2000).

Some surgeons have made modifications with more extensive cryoablation (Kosakai 1994). In theory, an approach exclusively using cryo- or RF-ablation would address the “Achilles heel” of maze surgery, that is bleeding from atrial sutures necessitating reoperation. On the other hand, Cox’s group report that reoperation for bleeding is nowadays “uncommon” in their center (Sundt 1997), but this might be related to vast experience. In an animal model, a non-cutting, RF-catheter ablation technique reduced the inducibility and duration of atrial fibrillation (Elvan 1995). When closed-chest RF-ablation in man proves to be effective (and safe), open-chest maze procedures might not be necessary anymore. “Hybrid-procedures” with open-chest cutting of the appendages, and cryo- or RF-ablation are being developed. Preliminary data indicate that such an approach might be successful and safe; of 78 patients undergoing intraoperative RF-ablation, 5% died in hospital while 69% were in sinus rhythm after a follow-up of 21±9 months (Beukema 1999).
Questions remain about the maze (III) procedure. The nature and origin of the postoperative sinus node problems might not be solely explained by the location of the sutures. Recently, it was shown that heart rate variability is depressed after the maze III procedure, but improves after 12 months (Pasic 1998), implying transient autonomic dysfunction. Presumably, the extensive cuts produce a degree of autonomic denervation with subsequent reinnervation over time. Another matter of debate is what “minimal” set of sutures will suffice. In an animal experiment, removal of the appendages with pulmonary vein isolation proved to be effective against the induction of atrial fibrillation (Fieguth 1997). The latter appears to be of crucial importance for success, presumably either by isolating foci or by modifying autonomic innervation. A reduction of the number of cuts is very appealing with respect to procedure simplification, and perhaps reduction of postoperative bleeding. In addition, less extensive cutting might (further) reduce sinus node dysfunction.

5. Hybrid therapy
Combination of therapies or “hybrid” therapy is another option (Van Gelder 1999b). Atrial fibrillation can be reduced to a flutter with a class Ic antiarrhythmic drug; subsequent radiofrequency ablation of the flutter circuit with continuation of the antiarrhythmic drug appears highly effective (Nabar 1999). Cardioversion success-rate can be enhanced by pre-treatment with antiarrhythmic drugs (Bianconi 1996, De Simone 1999, Oral 1999). Other possibilities are preventive atrial pacing with continuation of antiarrhythmic drug therapy or an atrioverter with preventive atrial overpacing. However, specific data on the feasibility of hybrid approaches are lacking.
References


Introduction


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