Summary and conclusions

Atrial fibrillation is a considerable problem both from an epidemiological and a clinical point of view. The arrhythmia carries substantial morbidity and also increased mortality. Unfortunately, no definite answer in terms of permanent restoration of sinus rhythm is available. Conventional arrhythmia treatment (antiarrhythmic drugs and cardioversion) is in the long run rather ineffective for most patients. More aggressive, surgical treatment is acceptable only in highly symptomatic patients or in patients already undergoing cardiac surgery. In addition, other unconventional (non-pharmacological) therapy such as the atrial defibrillator seems not suited as a general approach. Perhaps it is not surprising that the generally poor results have led to the opinion of many physicians “to digitalize and forget” since all effort to restore sinus rhythm is frustrated. Consequently, “rhythm-control” therapy is withheld from many elderly patients.

The management of the arrhythmia may be inadequate because we simply do not sufficiently understand the involved pathophysiological mechanisms. Many patients develop the arrhythmia in the absence of underlying disease and it is unclear what line of pathophysiological events has led to the arrhythmia. Other patients distinctly develop atrial fibrillation in the setting of underlying disease challenging the atria. Evidently, adequate treatment of underlying disease might reduce the arrhythmia in these cases but should start early to avoid arrhythmogenic structural alterations. Still, it has become increasingly clear that atrial fibrillation may reinforce its own electrophysiological basis especially at the very beginning of the disease (“atrial fibrillation begets atrial fibrillation”). Moreover, this important process is just a part of remodeling of the atria in response to atrial tachycardia. Many other determinants promoting atrial remodeling have been identified, including increased levels of neurohormones, ion channel alterations, subcellular changes, cellular dedifferentiation, and finally, apoptosis and necrosis.

Understanding why these changes occur, their time course, and their impact on the reinforcement of atrial fibrillation will hopefully direct interventions aimed at preventing and treating atrial remodeling. Clearly, the ultimate goal is to effectively restore and maintain sinus rhythm. This thesis addressed both fundamental and clinical issues of human atrial fibrillation in an attempt to
improve our insight in the intractability of the arrhythmia.

Until now, most data on atrial electrical remodeling come from animal experiments, partly fast atrial pacing models mimicking atrial fibrillation, partly from models using artificially induced atrial fibrillation. Data on the time course of atrial electrical remodeling in spontaneous, naturally occurring atrial fibrillation were lacking. In appendix 1, atrial remodeling in man was investigated with a focus on electrophysiology. Patients undergoing elective cardiac surgery with either persistent atrial fibrillation, paroxysmal atrial fibrillation, or sinus rhythm were compared for atrial refractoriness during the actual operation. The effective atrial refractory period was shortened in preoperative persistent atrial fibrillation. In patients with paroxysmal atrial fibrillation, the shortening of refractoriness was inversely proportional to the preoperative duration of sinus rhythm. This shortening of the atrial refractory period is presumably the cause rather than the consequence of the arrhythmia since all patients had paroxysmal atrial fibrillation of too short duration to provoke substantial electrical remodeling. By contrast, a short atrial refractory period during surgery was not predictive for the occurrence of postoperative atrial fibrillation. Furthermore, mitral valve regurgitation seemed to prolong refractoriness. Presumably, chronic atrial stretch induces this relative increase in refractoriness.

The cardiovascular system has many regulatory mechanisms trying to maintain stable hemodynamics. A pivotal role is fulfilled by cardiovascular neurohormones that are produced by several systems, including the natriuretic peptide system, the renin-angiotensin system, and the adrenal gland system. These systems come into action when hemodynamics are compromised, for example in the presence of heart failure. On the level of the heart, receptors are stimulated by these neurohormones, influencing myocyte function (such as contractility and electrophysiology) and morphology (for example cellular dedifferentiation, fibrosis, apoptosis, and necrosis). Appendix 2 dealt with mRNA expression of the natriuretic peptide system in the right atrial appendage in relation to atrial fibrillation. In patients with paroxysmal atrial fibrillation, no changes were present as compared to patients with sinus rhythm. Patients with persistent atrial fibrillation, however, showed distinct alterations in mRNA
content, irrespective of valve disease. This implies that atrial fibrillation is an independent stimulus for the expression of mRNA involved in the neurohormonal status of the atria. In appendix 3, we demonstrated in patients with advanced heart failure that atrial fibrillation was associated with higher levels of plasma endothelin and atrial natriuretic peptide, as compared to those in sinus rhythm. It could be argued that endothelin release (vasoconstrictive compound) is triggered by an increase in atrial natriuretic peptide level (vasodilating properties), but this is speculative. Since excessive neurohormonal activation in general is associated with a worse hemodynamic situation and clinical outcome, these results warrant further study on the impact of atrial fibrillation on (atrial and ventricular) myocyte function and molecular adaptations on the one hand, and patient morbidity and survival on the other. Further to the above, autonomic activation affects quality of life. Appendix 4 addressed quality of life in relation to autonomic nervous state in paroxysmal atrial fibrillation. It was shown that patients with paroxysmal atrial fibrillation had a significant impairment of quality of life, even in the absence of structural heart disease. In addition, depressed autonomic function was strongly associated with impaired quality of life. The results implicate that in addition to the impact on atrial fibrillation itself, the autonomic nervous system also determines the patients' well being.

In appendix 5, the common intersection of atrial fibrillation and heart failure was reviewed. On the one hand, atrial fibrillation occurs in the setting of preexistent heart failure. On the other hand, atrial fibrillation may promote heart failure. Both mechanisms may be present in the same patient and it is sometimes not clear which came first. In any case, striving for adequate rate-control during the arrhythmia is of utmost importance. Additionally, appropriate treatment of heart failure is very important, in particular when cardioversion therapy is considered. In drug refractory cases, AV-node ablation with permanent rate-responsive ventricular pacing may be considered. At present, it is unsettled whether the latter treatment should be offered in general. Nevertheless, cardioversion therapy is still considered a first line measure and we explored its usefulness. In appendix 6, the outcome of serial electrical cardioversion therapy with a focus on heart failure was described for a large cohort of patients with persistent atrial fibrillation. Serial electrical
cardioversion combined with serial antiarrhythmic drug therapy was rather unsuccessful in terms of preventing heart failure and maintenance of sinus rhythm. In addition, these failures occurred more often in patients with higher NYHA classes. Although this may seem rather obvious, and in line with the clinical experience of many physicians, it does not prove that rate-control therapy is just as good. A randomized comparison is needed to draw more definite conclusions. Therefore, the results of this study provide the rationale for the “RACE” study. This Dutch study entails a randomized comparison of serial cardioversion therapy versus rate-control therapy. The primary endpoints comprise morbidity (including heart failure, thromboembolism, and bleeding) and quality of life. **Appendix 7** continued with the feasibility of cardioversion therapy, investigated in a small group of selected patients with heart failure and persistent atrial fibrillation. As expected, the results were rather disappointing in terms of maintenance of sinus rhythm. However, treatment before cardioversion with ACE-inhibition may increase the immediate likelihood of successful cardioversion. The study does not warrant indiscriminate electrical cardioversion of every heart failure patient. Acceptance of the arrhythmia, amiodarone as initial antiarrhythmic drug, or alternative treatment should also be considered.

A final option in the treatment of (medically refractory) atrial fibrillation is atrial arrhythmia surgery. Many are reluctant to take this step, but patients with atrial fibrillation undergoing cardiac surgery for another reason are logical candidates. In **appendix 8**, we investigated patients with mitral valve disease and preoperative atrial fibrillation who underwent mitral valve surgery combined with a simplified Cox-maze procedure or “mini-maze”. The latter is not as extensive as the original procedure and consequently takes less time. A comparison was made between the aforementioned patients and patients in sinus rhythm as well as a historic group of patients with preoperative atrial fibrillation, both undergoing isolated mitral valve surgery. The results one year after surgery were encouraging, mini-maze patients showing comparable sinus rhythm, sinus node function, and exercise tolerance as compared to those with preoperative sinus rhythm. In addition, left atrial function returned in the majority of mini-maze patients. In spite of these favourable findings, atrial arrhythmia surgery is often associated with postoperative disturbances in sinus...
node function. **Appendix 9** dealt with the characteristics of rhythm after atrial arrhythmia surgery. Patients with preoperative atrial fibrillation undergoing maze surgery exclusively or combined (with a mitral valve intervention) were compared with patients in sinus rhythm either undergoing coronary artery bypass surgery or mitral valve surgery. Using an integrated approach, postoperative rhythm was explored with exercise tests, 24-hour ambulatory electrocardiography (including heart rate variability analysis), and non-invasive autonomic function testing. Cardiac surgery seemed to initially depress sinus node function, but improvement occurred in the consecutive 12 months. There was a marked attenuation of heart rate variability and vagal modulation of sinus node function which was not confined to maze surgery since it also applied to isolated mitral valvular surgery. These side effects were less pronounced or absent after coronary artery bypass surgery. We speculate that cutting the atria induces a degree of autonomic destruction, which improves but does not normalize within the year following surgery. Subsequently, it might be postulated that the above mentioned autonomic alteration contributes to the efficacy of maze surgery.

**Clinical implications and future directions**

This clinically oriented and mainly descriptive thesis on human atrial fibrillation illustrates several consequences of the arrhythmia that in turn correlate with difficulties in rhythm-control management. Although it is demonstrated that distinct changes on electrophysiological and neurohormonal levels occur, their exact pathophysiological role remains to be clarified. Therefore, future research should focus on changes on a cellular level, including (stretch activated) ion channel expression, cellular calcium handling, cellular neurohormonal status in terms of neurohormone production, receptor density, growth regulation and interaction between myocytes and non-myocytes, the time course of cellular adaptation and dedifferentiation, and the time course until the occurrence of irreversible cellular damage. In addition, clinical studies on how to prevent, reverse or attenuate these processes with pharmacotherapy (for instance with calcium antagonists or angiotensin II receptor blockers) or with more aggressive rhythm-control (for example TEE-guided cardioversion as soon as atrial fibrillation occurs or recurs) will be necessary to test the concept that reversion of atrial remodeling may improve sinus rhythm maintenance.
Hopefully, these efforts will turn atrial fibrillation into a less intractable arrhythmia. However, measuring quality of life in these clinical studies is mandatory to assess the impact on the patient. It is not unlikely that new, invasive, and even aggressive rhythm-control strategies will not improve quality of life. The same perhaps applies to atrial arrhythmia surgery, which is effective, but seems not very suitable for most patients since it concerns a major operation. Therefore, comparing different treatments (rate-control, conventional rhythm-control, unconventional rhythm-control, and surgical rhythm-control) with a focus on quality of life is urgently needed.

At present, many questions remain unresolved, but the elements contributing to the pathophysiology of the arrhythmia are becoming increasingly evident. As a result, a more effective treatment of atrial fibrillation can be expected in the next decade.