It has been recognized, that variations in heart rate during sinus rhythm are related to the interplay between cardiac function and the regulatory mechanisms governing cardiovascular function. Methods have been developed to analyze these variations in heart rate. In several experimental and clinical studies, heart rate variability (HRV) analysis has been shown to provide insight into autonomic control of the heart. More specifically, measures of HRV have been found to give information on sympathetic and parasympathetic influences on heart rate. Autonomic dysfunction is thought to play an important role in the development and progression of many cardiovascular disorders. This, in combination with the growing availability of the technique, have resulted in increasing attention for HRV analysis during recent years. The aim of this thesis was to investigate the potential clinical value of HRV analysis and to address some of the problems which may limit the clinical implementation of HRV analysis (chapter 1).

In chapter 2, mechanisms governing heart rate and the currently used methods of HRV analysis are reviewed. The techniques used for HRV analysis are basically divided into three methods, the time domain analysis, frequency domain analysis and non-linear techniques. These different techniques are reviewed and guidelines for the implementation and interpretation are discussed. In general, time domain parameters may serve as general measures of HRV, whereas frequency domain parameters may provide more specific information on the physiological mechanisms governing heart rate fluctuations. Only the combined evaluation of frequency domain parameters both in absolute and normalized units will provide adequate information to assess the contribution of sympathetic and parasympathetic modulation of heart rate. The clinical value of non-linear techniques requires further study.

In chapter 3, studies on the association between autonomic control and the occurrence of myocardial ischemia, both symptomatic and asymptomatic ('silent'), are reviewed. In the study described in chapter 4, this association is examined in more detail. HRV was studied in patients with signs of myocardial ischemia during daily life. In these patients, the occurrence of myocardial ischemia was found to be associated with a shift of autonomic balance towards sympathetic activation and was inversely correlated with measures of cardiac vagal control. The role of autonomic modulation was further substantiated by the changes observed after therapy with the β-blocker bisoprolol, which may in part explain the efficacy of β-blocker therapy in the treatment of myocardial ischemia. In chapter 5, we investigated whether analysis of HRV may be used to predict the efficacy of drug treatment in myocardial ischemia. It was observed, that especially patients with low HRV at baseline responded to treatment with the β-blocker metoprolol. HRV at baseline, however, could not be used to predict the efficacy of treatment with the calcium-antagonist diltiazem. These results therefore indicate, that analysis of HRV may be useful in selecting patients who will benefit from treatment with β-blockers.

In chapters 6 to 11, the results of studies on HRV in patients with chronic heart failure (CHF) are discussed. The studies reviewed in chapter 6 indicate, that HRV analysis provides useful information in CHF patients. HRV parameters have been shown to correlate with the degree of neurohumoral activation in CHF patients and HRV has been shown to have prognostic value in these patients. In chapter 7, the relation between measures of HRV and both clinical and neurohumoral parameters was examined in patients with mild to moderate CHF. In these patients with early stages of CHF, impairment of autonomic control was already observed as indicated by HRV analysis. Several statistically significant correlations were observed between HRV on the one hand and clinical and neurohumoral parameters on the other. For clinical purposes, however, it should be realized, that these correlations are rather weak. In chapter 8, cardiac autonomic dysfunction was studied in patients with early, untreated stages of CHF. Already a small but significant progression of disease was observed over 3-6 months, as reflected by a deterioration in clinical parameters, neurohormone concentrations and HRV, especially of HRV parameters associated with cardiac vagal control. In chapter 9, the effects of digoxin and ibopamine on HRV were assessed in CHF patients. Treatment with digoxin was found to prevent progressive deterioration in HRV, treatment with ibopamine only revealed non-significant trends. The changes in HRV induced by digoxin treatment paralleled the observed decrease in neurohumoral activation. Digoxin treatment was found to enhance cardiac vagal tone especially in the setting of neuroendocrine activation. In chapter 9, the effects of treatment with angiotensin-converting-enzyme (ACE) inhibitors on HRV were examined in CHF patients. ACE inhibition enhanced cardiac vagal tone both during night- and daytime, and partly restored the abnormal circadian pattern of HRV in CHF patients. In addition, it was observed, that especially patients with reduced cardiac vagal control at baseline responded with an enhancement of HRV after treatment. The results of this study indicate, that HRV analysis may be used to select patients with CHF who will especially benefit from treatment with an ACE inhibitor. Finally, in chapter 12, the prognostic value of HRV parameters was assessed in patients with early stages of CHF. In this study, specifically the prognostic value of Poincaré plots was examined, a representation of the non-linear properties of variations in heart rate. HRV, as assessed by these Poincaré plots, was found to have independ-ent prognostic value in patients with early CHF, and identified an increased risk for all-cause and sudden cardiac death.

In conclusion, analysis of HRV provides useful information on autonomic control in cardiovascular disease. At present, its clinical value is recognized for risk assessment after acute myocardial infarction and for early detection of diabetic neuropathy. The results of the studies described in this thesis indicate, that assessment of HRV may also be of value in patients with myocardial ischemia and CHF. These studies suggest, that HRV analysis may be used to identify patients who will especially benefit from specific treatment regimens, in particular treatment with drugs which have modulating effects on cardiac autonomic control. Still, many large scale studies will be needed to further establish the clinical value of HRV analysis.