SUMMARY

The aim of this thesis was to evaluate the relation between impairment of HRV (as parameters of autonomic dysfunction) in patients with CHF and the severity of the disease, and in addition the prognostic value of HRV impairment and severe ventricular arrhythmias in CHF patients was examined (chapter 1-3). Further, we studied and compared the differences between the effects of various drugs on different clinical, neurohumoral and HRV parameters (chapter 4-7). In chapter 8 the currently used drugs for CHF treatment were reviewed, with regard to their long-term effects in CHF patients.

In chapter 1 the results of a study including 79 patients with NYHA I-IV CHF due to ischemic heart disease are presented. In this paper the relations between severity of CHF (as documented by clinical and hemodynamic parameters) on the one hand, and HRV changes on the other were analyzed, with a description of the correlations between different HRV parameters and NYHA CHF class, left ventricular ejection fraction and peak VO2. In this study several significant correlations were found between NYHA CHF class, left ventricular ejection fraction, peak VO2 and HRV, with the interesting finding of a strong relation between HRV parameters and the most powerful clinical predictor of CHF mortality, peak VO2. The results suggest, that HRV may be used as (another) clinical indicator of disease severity in CHF.

From this study the question rose, whether impairment of HRV may also provide prognostic information in CHF, especially with respect of mode of death in these patients. In chapter 2 the correlation between cardiac mortality and HRV impairment was analyzed in a group of 173 patients with left ventricular dysfunction and CHF to find the predictive value of different HRV parameters. Of the analyzed HRV parameters, decreased SDNN and pNN50 were found to have an independent predictive value for all-cause cardiac mortality. While increased risk of sudden cardiac death could not be predicted by any of the studied HRV variables, impairment of pNN50 and decreased low frequency power were found to be strongly related to increased risk of death due to progressive pump failure. These results suggest, that time domain and frequency domain HRV parameters are essentially indicators of CHF severity, and as such, may provide basic prognostic information in CHF, but not specifically for sudden cardiac death.

In chapter 3, the predictive value of different types of ventricular arrhythmias for cardiac mortality during 24 hour ambulatory ECG monitoring was evaluated in 211 CHF patients with stable CHF. The primary finding of this study was, that although ventricular tachycardias were predictive for all cause cardiac death, the risk of sudden cardiac death was significantly increased in patients having faster and longer ventricular tachycardias, which may be representative of an enhanced adrenergic drive in these patients. In this paper the suggestion is made, that as sympathetic activation may be an underlying factor of life-threatening arrhythmias and increased mortality in CHF, estimation and reduction of cardiac sympathetic activation may be important in the risk assessment and treatment of CHF, respectively.

As physicians increasingly realized the causal relation between neurohumoral activation and disease progression, new drugs with neurohumoral inhibitory

properties achieved growing attention in the treatment of CHF. In part III, the long-term effects of different neurohumoral modulating drugs in CHF were evaluated.

In chapter 4 an observational mortality analysis is presented, which was conducted in 85 patients with sustained ventricular tachycardias or ventricular fibrillation, and depressed left ventricular function. In this study, drug treatment was guided by results of programmed electrical stimulation. The results showed the independent beneficial value of long-term β-blocker therapy on prognosis in patients with ventricular dysfunction and severe arrhythmias. However, whether the reduction in mortality caused by β-blockers was due to a reduction of the arrhythmogenic effects of elevated levels of serum catecholamines, or primarily to anti-ischemic effects, is not clear, and further studies are needed on this issue.

In chapter 5-8, the autonomic and neurohumoral modulating effects of different CHF drugs were studied, with special interest in therapy induced modifications of HRV. As indicated in the Introduction, in the last years, analysis of HRV has been used in the non-invasive evaluation of drug induced autonomic changes, and as such as a surrogate end-point for drug efficacy in CHF. However, since HRV changes are related to changes in hemodynamics, the object of these studies was to focus on comparison between HRV, neurohumoral and hemodynamic modulating effects of various CHF drugs.

In chapter 5, the clinical and autonomic effects of long-term metoprolol treatment in 24 patients with clinically stable, mild CHF were evaluated. In this study a discrepancy between the clinical and autonomic effects of long-term β-blocking therapy was observed. While after 6 months treatment there were no effects of metoprolol on exercise parameters, an improvement of some of the studied autonomic parameters (HRV variables and autonomic function tests) was seen, although most of these effects did not reach statistical significance. The observed trend of improvement of autonomic tests and HRV was suggestive of a correction of the sympathetic / parasympathetic imbalance and an improvement of the depressed vagal tone, without any change in serum norepinephrine.

In chapter 6 the results of a study evaluating hemodynamic and autonomic effects of a relatively new phosphodiesterase inhibitor -saterinone- during short-term infusion are presented. In this study, which included 36 patients with NYHA III-IV CHF, saterinone was found to have convincing vasodilating properties during 3 hours infusion, which was (in part) at the expense of an increase in heart rate. Interestingly, these hemodynamic changes were not accompanied by increase in serum norepinephrine or impairment of HRV parameters.

In chapter 7 the clinical and autonomic effects of long-term ibopamine treatment were evaluated. In this study, which was conducted in 59 optimally treated, primarily NYHA III CHF patients (added to ACE-inhibitor, diuretics and digoxin), ibopamine was not found to have a significant effect on exercise parameters or serum levels of neurohormones, although HRV analysis suggested an improvement of the autonomic function. Primarily HRV variables, that reflect vagal tone, improved, suggestive of a beneficial effect of ibopamine on the parasympathetic dysfunction.

In chapter 8 a review on the influence of various drugs on CHF mortality is given. This paper provides a compilation of the drug induced alterations in CHF

mortality of the last decades. As pointed out in this chapter, the currently established, optimal therapy of CHF includes ACE-inhibitors, diuretics, and digoxin. Recent studies with β-blockers and (to a lesser degree) with some calcium channel blockers suggest, that these drugs may also gain a role in the treatment of patients with left ventricular dysfunction and CHF. In this respect it is important to note, that drugs which are proven to have beneficial long-term effects in CHF patients, were also found to have either a beneficial or neutral effect on neurohumoral parameters. On the other hand, a favorable effect on neurohormones / HRV does not necessarily lead to a long-term beneficial effect, suggesting that other factors still play an important role (Introduction, Table III).

CONCLUSIONS

In the observational studies presented in this thesis, which were conducted in patients with clinically stable CHF, a significant correlation between impairment of HRV and disease severity was found. Furthermore, impaired HRV was demonstrated to have prognostic value for all cause mortality in CHF patients, although time domain and frequency domain parameters of HRV were not found to have any role in the prediction of sudden cardiac death.

In the drug intervention studies of the thesis, the induced hemodynamic, neurohumoral and HRV modifications were compared, with focus on the value and interpretation of drug induced HRV changes. In 2 studies with metoprolol and ibopamine, trends toward improvement of HRV were observed during drug treatment, in the absence of beneficial hemodynamic or neurohumoral effects. In the case of saterinone, HRV remained unchanged, while hemodynamics improved and positive chronotropic effects of the drug were observed during saterinone infusion. The observed lack of correlation between HRV modifications, and hemodynamic and neurohumoral drug effects in these studies suggest, that although HRV may be used to measure autonomic dysfunction in CHF, its value in the evaluation of drug induced autonomic changes is limited, at least in these groups of optimally treated CHF patients. Consequently, drug induced HRV changes need to be interpreted with caution, and physicians should take several other clinical and neurohumoral factors also into account, when evaluating drug effects in CHF. One important aspect in this regard is, that some drugs are apparently able to improve HRV, while at the same time they exert positive chronotropic effects. Combination of these effects is paradoxical, and the increase of heart rate is obviously not beneficial in CHF. Therefore, drug induced changes of heart rate should be also integrated in the standard analysis of HRV.

The studies presented in this thesis show, that neurohormones and HRV are good measures of CHF severity and mortality. However, with regard to evaluation of drug effects, the value of autonomic parameters is less clear in patients with optimally treated, stable CHF. The value of these parameters may be limited by several drug induced factors, that are not reflected by plasma neurohormones or HRV changes. Plasma neurohormones and HRV analysis alone therefore do not appear to be reliable, as surrogate end-points in the long-term drug evaluation of optimally treated CHF patients.