Value of neurohormonal and autonomic parameters for the assessment of the severity and prognosis in chronic heart failure
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SUMMARY AND FUTURE PERSPECTIVES
SUMMARY

Part 1 Introduction
The introduction provided background information concerning the neurohormonal and autonomic changes in patients with CHF. The main parameters for the assessment of neurohormonal activation and autonomic dysfunction were also briefly addressed.

The aim of this thesis was threefold:
1. to evaluate diagnostic tools to monitor patients with CHF
2. to study the progression and prognosis of CHF
3. to study drugs which are considered to have an effect on the autonomic and neurohormonal profile of patients with CHF

Part 2 Monitoring heart failure
Appendix 1
Anthracyclines are widely used in patients with breast cancer, but even low doses may cause left ventricular dysfunction. Although both diastolic and to a lesser degree systolic dysfunction were observed, autonomic abnormalities may possibly precede these changes and thus be a sensitive marker. Therefore, autonomic function (using HRV analysis) and diastolic function (using echocardiography) were studied in asymptomatic females with normal left ventricular systolic function who were treated with anthracyclines for breast cancer. The mean time interval for these assessments after the end of chemotherapy was 29 months. The results demonstrated that one or more diastolic parameters were abnormal in 50 % of the patients. However, HRV analysis demonstrated that autonomic function was impaired in 85 % of the patients. In conclusion, autonomic impairment occurs in a large proportion of asymptomatic patients with normal systolic function after high-dose anthracycline-based chemotherapy. In particular, HRV analysis may potentially be a sensitive tool to identify first signs of cardiotoxicity in these patients

Appendix 2
Since the introduction of commercially available kits for measurement of natriuretic peptides, new possibilities have emerged to study the neurohormonal profile of CHF patients. The purpose of this study was to validate a rapid BNP assay, measuring BNP levels in whole blood within minutes. We compared a new rapid BNP assay with a well-established conventional laboratory method for measurement of BNP levels in plasma. Secondly, BNP levels were compared with standard clinical parameters (NYHA functional class, LVEF, echocardiography and peak oxygen consumption) used to assess the severity of CHF. The new rapid BNP assay correlates reliably with the conventional measurement of BNP levels. In the higher ranges (>200 pmol/l), however, correlations were less close, and tended to overestimate. Furthermore, the results of the rapid BNP assay were strongly related to clinical parameters of CHF. In conclusion, the results indicate that BNP levels can reliably be measured by using a rapid and direct BNP assay. Secondly, rapid measurement of BNP levels correlates well with currently-used clinical tests to assess the severity of CHF.

Appendix 3
The neurohormonal and hemodynamic responses to lower body negative pressure were presented comparing CHF patients and healthy controls. Unloading of the cardiopulmonary baroreceptors by lower body negative pressure caused neurohormonal activation in the healthy controls, and arterial blood pressure was thus maintained. In contrast, neurohormonal activation was already present at baseline in the CHF group, and these patients failed to develop an additional neurohormonal response after lower body negative pressure. As a result, they were unable to maintain arterial blood pressure. These results provide new information regarding the impact of these activated systems on hemodynamic balance in patients with CHF.

Appendix 4
The hypothesis was tested that atrial natriuretic peptide plasma concentrations in patients with CHF decrease in cases of concomitant longstanding atrial fibrillation due to atrial degeneration. Patients with advanced CHF and chronic atrial fibrillation were studied retrospectively. Plasma concentrations of norepinephrine, renin, aldosterone and endothelin were not related to the duration of atrial fibrillation. In contrast, patients with severe left ventricular dysfunction were characterized by an inverse relation between the duration of atrial fibrillation and plasma concentrations of atrial natriuretic peptides. Apparently, in patients with advanced CHF with low LVEF, plasma ANP and N-ANP concentrations decrease during longstanding AF. This finding agrees with the concept that longstanding AF leads to impaired ability of the atria to produce these neurohormones due to inherent degenerative changes.

Part 3 Progression of heart failure
Appendix 5
CHF is characterized by increased neurohormone concentrations. Until now, the prognostic value of neurohormones in CHF had not been evaluated. The aim of the present study was to examine the relationship between 10 different plasma neurohormones (renin, aldosterone, norepinephrine, epinephrine, dopamine, endothelin, ANP, N-terminal ANP, BNP) and survival in 372 patients with advanced CHF. During follow-up 52 % of the CHF patients died, most of them due to progression of CHF or sudden cardiac death.
Although all plasma neurohormones were associated with mortality, natriuretic peptides (ANP, N-terminal ANP, BNP) were the most reliable independent prognostic factors.

**Appendix 6**
The aim of the present study was to examine whether the presence, or development of AF in patients with CHF, is associated with poorer prognosis, as compared to patients with SR and CHF. We studied 409 patients with moderate to severe CHF during long-term follow-up. In the study group, the majority of deaths were due to progression of CHF (55%) or sudden cardiac death (28%), but there was no difference in cause of death between SR and AF patients. Although overall mortality was higher in CHF patients with AF, AF was not an independent predictor of mortality. Of the patients who had SR at baseline 9% developed AF during the study. During follow-up, mortality in patients with SR was similar to that in patients with AF. These results support the notion that AF is common in CHF patients and that CHF patients are at risk for developing AF. The present data do not support the concept that the presence or development of AF is independently related to an adverse outcome during long-term follow-up.

**Part 4 Intervention in heart failure**

**Appendix 7**
CHF is accompanied by autonomic impairment and analysis of HRV is a well-accepted method to examine autonomic modulation of heart rate. In the present placebo-controlled study the autonomic effects (using HRV analysis) of a selective calcium channel blocker, mibefradil, were studied in patients with mild CHF. HRV analysis was performed at baseline and after 7 months of treatment. Although, a small but significant decrease on heart rate was found in the mibefradil group, HRV was not affected by treatment. In conclusion, mibefradil does not impair autonomic balance and in fact reduces heart rate in CHF patients.

**Appendix 8**
The clinical and autonomic effects of long-term metoprolol treatment in 24 patients with mild CHF was studied. In this study a discrepancy between the clinical and autonomic effects of β-blocking therapy was observed after 6 months of treatment. Although no effect on exercise capacity or plasma norepinephrine levels was observed after 6 months of treatment, an improvement of some of the studied autonomic parameters (heart rate variability and autonomic function tests) was found. Recent large-scale trials provided evidence for the add-on treatment with beta-blockers in CHF patients and our results further substantiate this, by the observed trend of improvement in autonomic balance. This was demonstrated by a correction of the sympathetic/parasympathetic imbalance and an improvement of the depressed parasympathetic tone, without any change in plasma norepinephrine levels.

**Appendix 9**
The hemodynamic and autonomic (using HRV analysis) effects of a new dopaminergic drug, CHF1035, are presented. In this study, which included 29 patients with clinically stable, mild to moderate CHF, 10 days of treatment with CHF1035 improved autonomic balance (i.e. improvement of almost all HRV parameters) and was found to have a decreased long-term effect on plasma norepinephrine levels. Interestingly, although only a small acute effect was observed on plasma atrial natriuretic peptide after drug treatment (possible related to cardiac unloading), no response (acute or long-term) was observed on all other plasma neurohormones. In conclusion, short-term treatment with the selective dopaminergic agonist CHF1035 reduces plasma norepinephrine concentrations and increases HRV parameters in patients with mild CHF.

**CONCLUSIONS**

Chronic heart failure can be monitored by the assessment of neurohormones, the analysis of HRV, and the use of lower body negative pressure. Plasma neurohormones are very reliable parameters to determine the severity of CHF since they provide information regarding the level of neurohormonal activation in these patients. The present thesis demonstrates that plasma neurohormones are closely associated with progression and prognosis of CHF, independent of the traditionally used parameters to characterize the severity of CHF (such as exercise capacity, LVEF and NYHA functional class). Furthermore, this thesis demonstrates that all plasma neurohormones measured, natriuretic peptides (i.e. ANP, N-terminal ANP, BNP) are the most reliable neurohormones for prediction of progression of CHF and determination of prognosis in these patients. However, the present results are only valid in the absence of AF. If patients with CHF also have AF, atrial natriuretic peptides become depleted and, as a result, assessment of these neurohormones has less value for monitoring progression of CHF and determination of prognosis.

Finally, we show the results of a new rapid BNP assay, which provides comparable results such as the ‘traditionally’ used assays in specific laboratories.
**FUTURE PERSPECTIVES**

Since CHF is a major medical, social and economical burden we should focus on early detection of CHF and the prevention of CHF progression. Therefore, monitoring these patients is very important in both the clinical and well as the outpatient setting and should preferably be performed by using simple, reliable, rapid and generally available tools. HRV analysis and measurement of baroreflex function is definitely of value but certainly not suited for widespread use. Instead, the use of neurohormones, in particular natriuretic peptides, appears to be very promising. Reliable, easy-to-use, and rapid kits are now commercially available to determine these neurohormones. The present thesis also suggests that natriuretic peptides are useful parameters for monitoring CHF progression and stratification of patients at risk for (sudden) cardiac death. Finally, the present thesis provides new ideas for using natriuretic peptides in clinical practice. Preliminary data have demonstrated that sequential measurement of neurohormones may provide reliable information regarding the clinical condition of CHF patients. ¹ Obviously, further studies are needed to prove the feasibility of performing sequential measurement of neurohormones. If these preliminary data can be confirmed in other studies, these measurements can be used to up-titrate or fine tune CHF patients with drugs that affect the neurohormonal system such as angiotensin-converting enzyme inhibitors, diuretics (including aldosterone receptor blockers), β-blockers or other cardiovascular drugs. In other words, a more appropriate target can be sequential measurement of neurohormones to guide drug treatment in patients with activated neurohormonal systems. This seems a new challenge for future research with neurohormones in the setting of CHF.

References