The arrhythmia risk profile in left ventricular dysfunction. The importance of neurohormonal activity and modulation
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SUMMARY

LV dysfunction is a common complication of myocardial infarction. The degree of LV dysfunction is positively correlated to increasing cardiac mortality. Cardiac mortality in patients with LV dysfunction can be subdivided into 2 modalities: progressive CHF and sudden death. This thesis deals with the risk of sudden death in patients with LV dysfunction. Apart from a reduced pumping function of the LV, several other factors occurring during the development of CHF are potentially arrhythmogenic. These include LV dilatation, neurohormonal activation and the presence of ventricular arrhythmias, either spontaneous or induced. Treatment of these patients is primarily aimed at preservation of LV function and prevention of arrhythmias, neurohormonal activation and ischemia. This thesis describes the patient at high risk for sudden death, who can be identified by studying LV function and volume, neurohormonal status and vulnerability for ventricular arrhythmias (appendices 1-5). Several kinds of intervention were studied as probes to investigate the multifactorial effects of pharmacological intervention in patients with LV dysfunction. These are described in appendices 6-10.

In appendix 1, the roles of the risk factors LV dysfunction, presence of arrhythmias and ischemia are reevaluated in view of the thrombolytic era. This report shows that successful thrombolytic therapy improves survival after myocardial infarction. If patency is obtained, it favorably affects two important risk factors. Both LV function and electrical stability are preserved by, in particular early, but also late patency of the infarct-related artery. Consequently, the development of two high risk factors after myocardial infarction is at least in part prevented. The third risk factor, recurrent myocardial ischemia or reinfarction, does not seem to be favorably affected by thrombolytic intervention. On the contrary, the reinfarction rate is increased by early thrombolytic therapy. The value of diagnostic tests remains unchanged after thrombolysis. Non-patency and abnormal autonomic control are relevant new risk factors. Persistent LV dilatation and HR variability, is described in appendices 2 and 3. After anterior infarction, recovery of HR variability parameters was most marked in patients who did not have increasing LV volume. By contrast, HR variability in dilators hardly improved, which was most clearly seen in the day-time hours. The identification of both higher concentrations of plasma norepinephrine before dilatation, and the reduction of day-time HR variability in the dilating group suggest at least a contributing role of the autonomic nervous system in the development of LV dilatation. The sympathetic nervous system remains activated after the infarct in patients with dilating LV.

Appendix 4 describes how VTs develop during conditions of altered autonomic control, i.e. physical exercise. In a total cardiologic population of 5842 patients, sixty (1.0%) patients developed 194 episodes of VT during exercise stress testing. Forty-two percent of these occurred during exercise and 58% during recovery. Two differ-
vent initiating electrocardiographic patterns were observed. In 17 (28%) patients VT was initiated by a short-long-short sequence of R-R intervals (group 1). Thirty-eight (63%) patients did not have this pattern of interval changes preceding VT (group 2). Five (8%) other patients showed both patterns. Clinical characteristics of the groups were different for angina and cardiomyopathy but not for previous myocardial infarction. In group 1, VT was related to recovery (76%; p<0.05). In group 2, occurrence of VT was equally divided between exercise and recovery. The electrocardiographic differences suggested that different initiating mechanisms are involved in the development of exercise-induced VT, which may enhance aimed antiarrhythmic therapy.

Appendix 5 reviews the value of HR variability analysis in patients with LV dysfunction. HR variability appeared closely related to the degree of neurohormonal activation and, to a lesser extent, to hemodynamic variables. Cardiovascular drugs may either stimulate or inhibit the degree of neurohumoral activation, and the effects of drug treatment on HR variability were in general consistent with their long-term effects in LV dysfunction and CHF.

In appendices 6 and 7, two novel antiarrhythmic drugs are studied in the context of LV dysfunction. The first, the class IC antiarrhythmic restacorin, did not affect hemodynamics in normal subjects, whereas in patients with LV dysfunction, a relevant worsening of hemodynamic parameters was observed. The second, the class III antiarrhythmic almokalant, did not cause autonomic changes in postinfarct subjects. Almokalant prolonged refractory periods and action potential duration, in particular at shorter pacing cycle lengths. The results also indicated absence of reverse rate-dependence. Therefore, our study confirmed that class I drugs are inappropriate in LV dysfunction. Class III agents appear more successful in LV dysfunction, although the clinically adverse proarrhythmic effects should be solved first, before widespread use of these agents can be recommended.

Appendix 8 describes the effect of acute hemodynamic improvement in patients with severe CHF. Treatment with a single dose of isomazole not only improved hemodynamics, but also improved HR variability. This study suggests that impaired autonomic cardiac control can be acutely improved by correcting hemodynamic abnormalities. Long-term effects of this drug can not be predicted or extrapolated from this study.

For twenty years, the beneficial effect of β-blockers on sudden death rate after myocardial infarction is well known. Appendix 9 details the relevance of lipophilicity of β-blockers. Previously, it has been reported that effects of β-blockers may be mediated by a central effect. Central administration of these drugs increased the threshold for VF. If this were true, it would change the concept of postinfarct treatment with β-blockers. In appendix 9 is described that lipophilic metoprolol acts similarly to hydrophilic atenolol with respect to HR variability. Not only during rest, but also during challenges such as physical exercise and mental load, both drugs behaved
the same. Compared to the drugfree period, both drugs increased HR variability during daily life and mental load. This shows that during normal daily life, the additional effect of lipophilicity of β-blockers is not apparent. Whether this also holds for conditions like emotional stress or acute ischemia needs to be investigated.

Angiotensin-converting enzyme inhibitors are widely used in patients with LV dysfunction. Prognosis of these patients is improved with ACE-inhibitors. This holds true particularly for prevention of progression of CHF. Since the effects of ACE-inhibitors on sudden death are less convincing, in appendix 10 we studied the effect of the ACE-inhibitor perindopril on the arrhythmia risk profile in patients with LV dysfunction after myocardial infarction. After 3 months treatment, the LV volume in perindopril patients had not increased, whereas in the placebo group it had increased significantly. Thus, perindopril prevented the occurrence of LV dilation after myocardial infarction. Arterial blood pressure was decreased in the patients with perindopril. Norepinephrine levels were equal. The beneficial effect of preservation of LV function was paralleled by an improved arrhythmia risk profile. Sustained arrhythmias in the perindopril group were induced at a later stage during the protocol. Induction of VF was lower in the perindopril group: 12% vs. 31%, but did not reach significance. Effective refractory periods in perindopril patients were slightly but consistently longer during all stages. Dispersion of refractoriness was significantly higher in inducible patients and was lower in the perindopril group: 25±17 ms in the placebo group and 17±11 ms in the perindopril group (p<0.05). From this study we conclude that chronic treatment with perindopril has mild direct antiarrhythmic properties in postinfarct patients with LV dysfunction. The antiarrhythmic effect was reflected by a reduction in induction of VF, a prolongation of the effective refractory periods and particularly a reduced dispersion of refractoriness. This effect of perindopril may contribute to a more homogeneous electrical circuit, which can be expected to improve prognosis.

CONCLUSIONS

The aims of the thesis were to identify the high risk conditions for sudden death and to investigate the effects of intervention, focusing on the interplay between LV dysfunction and neurohormonal activity. The patient at high risk for sudden death has an importantly impaired LV function and a dilated LV, which forms a potential substrate for arrhythmias. Sustained changes in neurohormonal control (low HR variability) are an important modulating factor. After myocardial infarction, the patient at risk can already be identified by a sustained low HR variability that does not improve during follow-up. This is paralleled by dilation of the LV. In the subacute phase, norepinephrine concentration in this patient is generally high compared to the patient in whom autonomic control is restored during follow-up. Effects of intervention can be assessed by close monitoring of HR variability. Drugs of which it is known that they improve long-term prognosis increase HR variability and vice versa.
The most relevant pharmacological intervention in patients with LV dysfunction is treatment with ACE-inhibitors. This thesis shows not only that treatment with perindopril preserves LV function, but also that the arrhythmia risk profile is favorably affected. β-Blocking agents are known for their favorable effect on sudden death rate in the postinfarct setting. The mechanism for this effect is not completely understood, but central effects of β-blockers still may play a role, despite the fact that we could not demonstrate a differential effect between lipophilic and hydrophilic agents. Differences may occur in particular during conditions like emotional stress and acute ischemia. Antiarrhythmics of class III, such as amiodarone and sotalol may be promising in LV dysfunction. Novel class III agents induce neither decline of LV function nor alterations in autonomic functions. Nevertheless, similar to class I agents, pure class III drugs have been shown recently to increase mortality in postinfarct patients with LV dysfunction.

Future pharmacological intervention in patients with LV dysfunction should take into account the multifactorial effects of drugs. In order to safely obtain preservation of LV function and prevention arrhythmias, new drugs for this indication should be studied in subjects with - at least - LV dysfunction. Then, hemodynamic and neurohormonal effects should be closely monitored. Future studies should assess whether lipophilicity is a relevant property of β-blockers during emotional stress or acute ischemia, with respect to occurrence of VF. Moreover, combinations of ACE-inhibitors, β-blockers and possibly class III agents may further improve the arrhythmia risk profile in LV dysfunction.