Heart failure, myocardial ischemia and neurohormonal activation
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Summary

Part I: Introduction and aims of the thesis.
In part I, a general introduction of the subject is given, and the aims of this thesis are explained. The first aim of this work was, to study whether the condition of CHF per se was associated with changes in myocardial perfusion, and whether this could be interpreted as ischemia. Given the importance of neurohormonal activation on CHF and ischemia, we further evaluated the influence of the 2 main neurohormonal systems.

Part II: Relation Heart Failure and Ischemia: Pathophysiology (chapter 1 and 2).
In the first two chapters, we describe two studies in which we examined myocardial blood flow and its reserve (and myocardial metabolism) in patients with CHF, by using positron emission tomography (PET). The data show that in patients with CHF, myocardial flow reserve is impaired and that this impairment is related to the severity of CHF. This holds for both patients with CHF due to idiopathic dilated cardiomyopathy (chapter 1) (who, by definition, have normal epicardial coronary arteries) and patients with coronary artery disease, in which we examined the non-infarcted, non-stenotic arteries (chapter 2). The data suggest, that the condition of CHF as such leads to an impairment of myocardial flow reserve, while resting myocardial flow was not affected. Also, a significant part of the myocardium showed a perfusion/metabolism mismatch, suggesting ischemia and/or hibernation (chapter 1). Moreover, we also observed ischemia-like responses during dobutamine stress echocardiography which were regionally matching the PET abnormalities, further supporting the concept of regional ischemia in CHF (chapter 2). The 2 studies thus suggest that the condition of CHF as such may cause myocardial ischemia.

Part III: Renin Angiotensin System and Pharmacological Intervention (chapter 3-6).
Recurrent myocardial ischemia and ischemia-related events are common after myocardial infarction. In the CATS study, we investigated both, and found no effects on exercise induced ischemia, but a reduction in ischemic events, most obvious after prolonged months of treatment (chapter 3). In chapter 4 we studied the effect of ACE inhibition on pacing-induced ischemia, both in patients with normal and in patients with impaired LV function. Anti-ischemic effects were most pronounced in patients with LV-dysfunction, possibly mediated by beneficial effects on ischemia-induced neurohormonal activation. Since the number of patients studied in this exploratory and mechanistic study was rather small, no definitive inference on the potential clinical benefit of ACE-inhibition on myocardial ischemia can be made. In another PET study (chapter 5), we observed that myocardial blood flow was already impaired in...
patients with asymptomatic, mild LV dysfunction, and coronary artery disease. The ACE-inhibitor perindopril showed a trend in preventing deterioration of endothelial dysfunction during 8 weeks treatment, as was derived from studies using the cold pressor test. However, drug-effects were only mild, which may have been related to the short treatment period, and the methodology used. In the TAPE study (chapter 6), we speculated, that in patients with coronary artery disease (and normal LV function at rest), exercise would (further) increase RAS activation, and lead to LV dysfunction (documented by increased natriuretic peptides), which could be blunted by ACE inhibition. The results showed, that 12 weeks treatment with enalapril, on top of beta-blockade, improved exercise-induced time to 0.1 mV ST-segment depression. There was a only a non-significant trend to lower levels of peak in ANP and BNP levels during exercise, however.

Part IV: Autonomic Nervous System and Pharmacological intervention (chapter 7 and 8).

In Part IV we studied both the effects of the sympathetic nervous system and its blockade (chapter 7) and that of the parasympathetic nervous system and its blockade (chapter 8). The results of chapter 7 indicate that in patients with normal LV function, the beta-blocker epanolol did not affect pacing-induced changes in coronary blood flow or coronary vascular resistance. In contrast, in the LV dysfunction group, the improvement in coronary sinus blood flow and reduction in coronary vascular resistance during pacing was inhibited by epanolol. This inhibition of the normal coronary vasodilating effects during atrial pacing coincided with more systemic neurohormonal activation after administration of epanolol during pacing-induced ischemia in LV dysfunction. No definitive inference on the potential clinical benefit that may be associated with epanolol in patients with ischemic LV dysfunction can be made because of the small size of the study. In chapter 8, we studied the effect of blockade of muscarinic receptors by atropine (=parasympathetic or vagal blockade) on myocardial ischemia. Since acetylcholine (muscarinic agonist) causes vasoconstriction in patients with endothelium dysfunction, it was speculated that atropine leads to vasodilatation in diseased endothelium. In LV dysfunction and CHF, vagal tone is decreased, and therefore we speculated that the effects of atropine would be attenuated in CHF patients. The results confirmed this, as the anti-ischemic effects of atropine were more pronounced in patients with coronary artery disease and normal LV function, compared to those with LV dysfunction.

Discussion/future study directions

The results of this work together suggest, that coronary flow abnormalities are present in patients with LV dysfunction and CHF, that these occur early in the disease, and that they are related to the severity of CHF. These flow abnormalities may lead to myocardial progression of this syn...

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More research is needed on the genetic and metabolic and possibly open new...
may lead to myocardial ischemia, and thus play a role in the pathophysiology and the progression of this syndrome.

Drug intervention, which blocks the RAS and the autonomic nervous system can be beneficial, and the window of benefit appears to be larger as CHF becomes more advanced, which agrees with clinical studies of ACE inhibitors and beta-blockers. The reverse is true for muscarinic blockade.

More research is needed to further study underlying mechanisms, including genetic and metabolic changes, which may provide more pathophysiological insight and possibly open new avenues of drug treatment in this devastating disease.