Influence of medical intervention on sympathetic activity in heart failure

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Chapter X

General discussion
and clinical implications
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Insight in pathophysiology and treatment of heart failure has changed tremendously during the last decades. The earliest haemodynamic concept of the pathophysiology of heart failure focused on the retention of water and salt whereas therapy was limited to the removal of fluid from the body. Although still valid, with the introduction of modern diuretics which are very effective to alleviate symptoms, it was recognized that the haemodynamic derangements alone do not solely explain the many features associated with the syndrome of heart failure. This encouraged further (and ongoing) search for other pathophysiological processes involved in heart failure. The fact that ACE-inhibitors and β-blockers are effective in reducing both mortality and hospital admissions underscores the importance of the neurohumoral concept in the pathophysiology of heart failure. The neurohumoral concept recognizes the importance of compensatory mechanisms (sympathetic activation, activation of the renin angiotensin system) as a consequence of a decreased cardiac output. Virtually all of these compensatory mechanisms, while being initially beneficial, have deleterious long-term consequences thus aggravating the disease process.

Other, more recently demonstrated pathophysiological mechanisms include cytokine and immune activation, ventricular remodeling and programmed cell death. In addition, the initial insult and subsequent clinical events like ischemia and atrial fibrillation deserve attention because they attribute to disease progression and offer secondary treatment options.

Although advancements are made in both pathophysiological mechanisms involved in heart failure and treatment modalities, the clinician is still confronted with a malignant disease with a 1-year mortality of approximately 50% in more advanced cases of heart failure.

Activation of the (cardiac) sympathetic nervous system plays a major role as a compensatory mechanism in heart failure. Non-invasive imaging and quantification of sympathetic activity with 123I-metaiodobenzylguanidine (MIBG) may guide the clinician to treat patients with all stages of heart failure.

Understanding pathophysiology

As in the present thesis MIBG imaging demonstrates derangements at the level of the sympathetic presynaptic neuron in heart failure. This in addition to the already known downregulation of the β-receptor on the myocyte and abnormalities in signal transduction. Exact mechanisms are not yet elucidated, prejunctional norepinephrine (NE) release is a complex interplay between sympathetic tone, NE release, re-uptake and spillover. NE release is facilitated by prejunctional β2 and angiotensin II receptors and inhibited by prejunctional α-receptors. Future research will be directed at visualization and quantifying these receptors. We and others demonstrated that enalapril and metoprolol increase cardiac MIBG uptake. This indicates that the beneficial clinical effects of β-blockers and ACE-inhibitors are accompanied by improvement of presynaptic sympathetic nerve integrity.
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Monitoring therapy
A non-invasive tool to identify responders to medical therapy (i.e. β-blockers and ACE-inhibitors) and to assess optimal dosing strategies would be most helpful. Unfortunately, no such tool is available. Although myocardial MIBG uptake improves after treatment with metoprolol and enalapril, large inter- and intraindividual variations exist. Moreover, no uniform quantification method has been developed making comparison between laboratories difficult. Therefore medical treatment with β-blockers and enalapril should be directed at the maximal tolerated dose in individual patients. Recent research demonstrated that B-type natriuretic peptide can probably be used as a simple noninvasive marker of the efficacy of medical treatment.

Prognostic markers and identification of high risk patients
More severe forms of heart failure are still associated with a very high mortality. ACE-inhibitors and β-blockers are of unequivocal benefit and can alter the biological properties of the heart in systolic dysfunction. Treatment of heart failure due to more dominant left-ventricular diastolic dysfunction remains an open question. Identification of high risk patients is important in managing for example a heart transplantation waiting list because of limited donor supply. We demonstrated that, among other clinical parameters, maximal oxygen consumption remains the most powerful predictor of mortality in patients with more severe forms of heart failure. Cardiac MIBG uptake as a marker of sympathetic activation has probably no additional value with regard to prognosis or risk stratification.

In conclusion, delaying the onset of heart failure and its progression is of major importance to the individual patient. Activation of compensatory mechanisms in heart failure in response to a decreased cardiac output plays an important role. Medical treatment with β-blockers and ACE-inhibitors interfere with these compensatory mechanisms and reduce both mortality and morbidity. Imaging and quantification of one of these compensatory mechanisms, cardiac sympathetic activity, with 123I-MIBG imaging is of limited clinical value in patients with heart failure but can contribute to the understanding of the pathophysiology in heart failure and other abnormalities of the heart.