Influence of medical intervention on sympathetic activity in heart failure

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Chapter I

Introduction
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Incidence, prevalence and mortality of heart failure

Improved treatment modalities for acute coronary syndromes and better primary and secondary prevention have shifted the spectrum of manifestations of heart disease into the direction of the syndrome of heart failure. Although data are limited, it is estimated that in a general population the incidence of heart failure is one to five cases per 1000 each year (data derived mainly from the Framingham Heart Study) with a steep increase with age. Prevalence data are more commonly available from different studies but vary greatly. Prevalence in the general population is estimated between 3 and 20 individuals per 1000. Among those aged 75 years or older, this estimate is between 80 and 160 persons per 1000.1

Despite considerable progress in the treatment of heart failure, mortality is still disappointingly high. Annual mortality for patients with chronic heart failure is about 10%, mortality in patients with more severe forms of heart failure is estimated between 15 and 40% per year depending on severity.2-5

The syndrome of heart failure

Heart failure may be viewed as a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functional cardiac myocytes, or alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally (figure 1). The index event may have an abrupt onset, like a myocardial infarction, it may have a gradual onset as is the case in hypertension or the exact mechanism is not known (idiopathic dilated cardiomyopathy). This initial insult may result in systolic and/or diastolic heart failure. Many compensatory mechanisms become activated in the setting of depressed cardiac output that are able to sustain and modulate cardiac output for a period of days to months to years depending on the severity of the initial insult. These compensatory mechanisms are able

Heart failure begins after an index event produces an initial decline in pumping capacity of the heart. Following this initial decline in pumping capacity of the heart, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin angiotensin system and the cytokine system. In the short-term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening LV remodeling and subsequent cardiac decompensation. As a result of worsening LV remodeling and cardiac decompensation, patients undergo the transition from asymptomatic to symptomatic heart failure.

to maintain cardiac output so that the functional capacity of the patient is preserved or is depressed only minimally, a condition in which the patient frequently adapts his physical activity. However, at some point in time, patients will become overtly symptomatic, probably with a resultant increase in morbidity (hospitalizations) and mortality. This transition to symptomatic heart failure is accompanied by further activation of neurohormonal and cytokine systems, as well as further left ventricular remodeling. Ultimately, heart failure will progress independently of the initial cause and independently of the hemodynamic status of the patient. Thus, advanced forms of heart failure should be viewed as a syndrome in itself.

Compensatory mechanisms in heart failure

Compensatory mechanisms in heart failure include activation of the sympathetic nervous system, and salt and water retaining systems (renin angiotensin system) as well as activation of vasodilatory molecules including natriuretic peptides, prostaglandines and nitric oxide (figure 2). In addition, other humoral compensation mechanisms are activated. Arginine-vasopressin has antidiuretic and vasoconstrictive effects that contribute to the increased cardiac filling pressures. Endothelin is a potent vasoconstrictor which is derived from the endothelial cells. Apart from its vasoconstrictor properties, it increases intracellular calcium and stimulates myocardial hypertrophy. These compensatory mechanisms are considered to be initially beneficial to maintain cardiac output but eventually aggravate the disease process with a further decline in cardiac function. Medical interventions interfering with these activated compensatory mechanisms have been shown to be beneficial by reducing both morbidity and mortality underscoring the fact that activated neurohumoral mechanisms play an important role in heart failure.

![Figure 2](image)

**Figure 2** The syndrome of heart failure
At some point in time, heart failure may progress independently of the cause and neurohormonal status of the patient and becomes a disease process by itself.
Treatment and future perspective in heart failure

Treatment of heart failure may be directed at relieving symptoms, improving quality of life, reducing hospitalizations, reducing mortality, delaying disease progression and (ideally) reversing the disease process.

Diuretics are known for many years and are very effective to alleviate symptoms of fluid retention in heart failure. However, they influence neither morbidity nor mortality and they do not influence the disease process. Nitrates, in combination with hydralazine, have been shown to reduce mortality. The role of either a nitrate or hydralazine is less clear. The converting enzyme inhibitors (ACE-inhibitors) have been conclusively shown to improve long-term prognosis in symptomatic and asymptomatic heart failure patients. In addition, ACE-inhibitors reduce hospitalization rates and delay the development of more severe heart failure. Digoxin has no effect on either overall or cardiovascular mortality rate but reduces the number of hospitalizations for worsening heart failure.

Digoxin generally produces a short-term improvement in symptoms. Angiotensin-I receptor blockers have been available for several years now and are registered for hypertension. Although treatment of heart failure with an AT-I receptor blocker on top of an ACE-inhibitor theoretically should offer some advantage their exact place in the treatment of heart failure remains to be established. At the present time, this class of drugs should probably be reserved for patients who cannot tolerate an ACE-inhibitor due to cough or other side effects because recent trials are not very convincing in demonstrating an additional effect of AT-1 receptor blockers. Spironolacton, a mild, potassium-sparing diuretic counteracting aldosteron, was recently shown to reduce mortality in more severe forms of heart failure. Finally, β-adrenergic receptor blockers have been shown to have beneficial effects in mild and more severe forms of heart failure on top of treatment with an ACE-inhibitor. A reduction of approximately 30% was seen in both morbidity and mortality.

Table 1 summarizes some new, experimental therapies for heart failure interfering with the neurohormonal and inflammatory responses in heart failure.

Apart from medical therapies that (1) reduce pre- and afterload of the left ventricle, (2) reduce volume overload and (3) interfere with the activated neurohormonal systems other treatment modalities like biventricular pacing, left ventricular assist devices and heart transplantation can

Table 1

Some new, experimental therapies for heart failure

| Endothelin (ET-1) receptor blockade (bosentan) |
| Central α, adrenergic and imidazole receptor stimulation |
| Natriuretic peptides (ANP and BNP) |
| Tumor necrosis factor and other cytokines antagonists (etanercept) |
| Vasopressin antagonist |
| Parasympathetic modulation |
| G-protein-coupled receptor modifiers (e.g. β ARK inhibitors) |
| Inhibitors of apoptosis |
offer additional benefit in more severe forms of heart failure. In the near future, the introduction of angiogenesis and myogenesis, aiming at reversal of the disease process may lead to dramatic changes in the therapeutic approach of heart failure.

**Purpose of this thesis**

Because sustained sympatho-excitation as compensatory mechanism in heart failure is maladaptive (thereby exerting detrimental clinical effects) and is correlated to prognosis, assessment of sympathetic nervous activity is valuable to predict clinical outcome and to evaluate the effect of therapeutic strategies in these patients. In addition, studies assessing cardiac sympathetic function will help us in understanding the syndrome of heart failure and the maladaptive consequences.

Sympathetic activation can be assessed in several ways. In this thesis, $^{123}$I-MetalodoBenzyl Guanidine (MIBG), a structural analogue of norepinephrine (NE) is used. MIBG has been shown to be taken up by sympathetic nerves in a manner similar to NE but it is not metabolized. Myocardial uptake can be visualized and quantified using a gamma camera and dedicated software. The aim of this thesis was to study the influence of β-blockers (metoprolol) and angiotensin converting enzyme inhibitors (enalapril) on cardiac sympathetic activation as measured by $^{123}$I-MIBG in patients with heart failure. In addition, the relation between myocardial MIBG uptake and several hemodynamic, clinical (including prognosis) and neurohormonal parameters was studied.

**References**


