PART 1

Introduction
INTRODUCTION

The phrase of “chronic heart failure” is often used and this suggests that it is well understood. However, controversy has always surrounded the use of this phrase. This is partly caused by advances in the understand of the pathophysiology, which have rendered insufficient earlier definitions. Furthermore, no single definition suffices because the clinical and physiological criteria differ. A practical definition is that CHF is “a clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses.” This definition implies that there should be an abnormality of the heart and that much of the clinical presentation is a consequence of the response of the body to the abnormal function of the heart.

The most common cause of CHF is no longer hypertension or valvular heart disease, as they were in past decades, but rather coronary artery disease. The long-term existence of specific risk factors and the presence of CAD will eventually lead to the development of CHF, as demonstrated in figure 1 (modified Braunwald circle). Despite significant progress in the prevention and treatment of cardiovascular disease in the past decades, the incidence and prevalence of CHF have been increasing steadily in recent years. Moreover, the prevalence and incidence of CHF is age dependent (figure 2): the incidence increases from approximately 1% in persons in their fifties to over 30% in persons older than 80 years. In normal individuals aging produces profound effects on the cardiovascular system. On an anatomic basis (figure 3), the most consistent cardiac change with aging is progressive left ventricular hypertrophy. This can be exacerbated by chronic hypertension and may eventually lead to CHF.

The prognosis of patients with CHF is poor with a mortality rate 6-7 times that of the general population. The mortality one year following the onset of CHF lies around 30%. There is no evidence to date that the prognosis of CHF in the community has improved despite advances in therapy over the last 4 decades. However, the effect of the widespread implementation of drugs that prolong life in patients with CHF may not yet have come evident on a population level. The observed increase in hospital admissions for CHF may seem paradoxical in view of the declining cardiovascular mortality and improvements in hypertension treatment in most countries in the developed world. The declining coronary artery disease mortality rates have been attributed mainly to a lower case fatality rate. It has also been suggested that the treatment of hypertension, as a major risk factor for developing CHF, merely postpones the onset of CHF to an older age rather than preventing it.

Besides CHF, atrial fibrillation is also common in the elderly. Owing to common risk factors including hypertension and left ventricular hypertrophy, both disorders are often present in the same patient. In addition, there is increasing evidence of a complex, reciprocal relation between CHF and atrial fibrillation. Thus, CHF may cause atrial fibrillation, electromechanical feedback and neurohumoral activation playing an important mediating role. In addition, atrial fibrillation may promote CHF; in particular, when there is an uncontrolled ventricular rate, tachycardiomyopathy may develop and thereby CHF. Eventually, a vicious circle between CHF and atrial fibrillation may form, in which neurohormonal activation and subtle derangement of rate control are involved. Although atrial fibrillation is associated with significant morbidity and mortality during follow-up, the prognostic significance of atrial fibrillation in the setting of CHF has not been fully elucidated.

Figure 1. The development of CHF. From risk factor to advanced CHF. CAD; coronary artery disease, LV; left ventricular, LVH; left ventricular hypertrophy.
Cardiac changes in the elderly. The left atrial cavity enlarges, and the left ventricular cavity becomes smaller. The amount of space available for the mitral leaflets decreases with aging (from Roberts WC, Ann Intern Med 1972)

**Figure 2.** Increased incidence of CHF with age (from Kannel and Belanger, Am Heart J 1991)

**Figure 3.** Cardiac changes in the elderly. The left atrial cavity enlarges, and the left ventricular cavity becomes smaller. The amount of space available for the mitral leaflets decreases with aging (from Roberts WC, Ann Intern Med 1972)
NEUROHORMONAL AND AUTONOMIC CHANGES IN CHF

The observation that CHF can progress independently of the hemodynamic status of the patient has focused interest on other possible mechanisms responsible for disease progression. As a result the neurohormonal hypothesis was formulated. 15 According to this hypothesis, CHF progresses because several endogenous neurohormonal systems, that are activated after the initial injury to the heart, exert a deleterious effect. 16 Such an effect may occur through either neurohormonally mediated hemodynamic deterioration 17 or through a direct toxic effect on the myocardium. 18 Both of these derangements may further increase neurohormonal activation and, over time, exacerbate the degree of secondary baroreceptor dysfunction. 19

The first trial testing the neurohormonal hypothesis was the CONSENSUS study. 20 The aim was to study whether enalapril, a drug which interferes with the renin-angiotensin-aldosterone system, would reduce progression of CHF. The results demonstrated a reduction in both mortality and morbidity. This study was performed in patients with severe CHF, but favorable results were later on also obtained in the SOLVD study and V-HeFT II study. 21,22 It can be speculated that these effects were related to peripheral vasoconstrictor effects (thus substantiating the hemodynamic concept), however, enalapril had the most profound effect in patients with the strongest neurohormonal activation. 22 Additional and intriguing evidence favoring the neurohormonal hypothesis emerged from clinical studies with drugs that block the activity of the sympathetic nervous system. Following the awareness that long-term sympathetic activation was deleterious for the heart 23 there was increasing interest in the use of β-blockers in the treatment of CHF. Although several small reports showed that β-blockers could cause acute worsening of CHF, 24-26 studies in Sweden in the early 1970s raised the possibility that long-term therapy with these drugs might produce hemodynamic and clinical benefits. 27,28 Additionally, the effects of β-blockers on mortality were studied. Although the effects on mortality were somewhat disappointing in the first small trials, 29,30 a profound positive effect was observed in large-scale CHF trials with β-blockers on top of ACE inhibitors on survival, progression of CHF, hospitalization and the incidence of sudden death. 31-33

NEUROHORMONAL AND AUTONOMIC PARAMETERS

Measurement of plasma neurohormones provides information about the extent of neurohormonal activation in CHF. The first parameter used was plasma norepinephrine level. Reports in the early 80s demonstrated that high plasma norepinephrine levels precede and predict the progression of CHF and death even in the patients with asymptomatic CHF (figure 4). 15,34-35 A plasma norepinephrine level of 400-800 pg/ml corresponds with an increased mortality risk; a level over 800 pg/ml predicts an even higher 1-year mortality risk due to progressive CHF. 15,34 Later on, other studies demonstrated that besides plasma norepinephrine, increased levels of angiotensin-II, and aldosteron correlated significantly with mortality in CHF. 36 With the introduction of natriuretic peptides kits new possibilities have emerged. 37,38 Indeed, natriuretic peptides have shown to be superior to traditional neurohormones in the assessment of clinical severity and prognosis. 39,40 Furthermore, their reproducibility is higher, 41 which make them even more useful in clinical practice. 42 It has been shown that BNP is the most sensitive marker in this respect. 39,43-45

Numerous studies have evaluated the autonomic nervous system in patients with CHF and have demonstrated a characteristic dysfunction of the sympathetic 46 and parasympathetic 47 limb and a deranged baroreceptor function. 48,49 Taken together, CHF is characterized by increased sympathetic drive and reduced parasympathetic tone. As a result of the increased sympathetic drive the myocytes of the failing heart lose their ability to respond to the β-adrenergic receptor agonists through a process of desensitization. 46 Desensitization is likely to be both beneficial and deleterious in patients with CHF. By reducing energy expenditure by the energy-starved myocardium, this adaptive response is beneficial; however, by reducing contractility and depressing the ability of the failing heart to increase its output in response to exercise, desensitization is also deleterious. The role of the parasympathetic system is not completely understood, but this system probably plays a role in inhibiting sympathetic outflow. In the setting of CHF this inhibitory effect is reduced. 50 Baroreceptors are the principal modulators of sympathetic and parasympathetic nerve activity and respond to changes in pressure (arterial baroreceptors) and volume (cardiopulmonary baroreceptors). 51,52 By regulating sympathetic and parasympathetic outflow from the brain stem, these baroreceptors provide an important control mechanism for vascular tone, heart rate and contractility, thus indirectly altering the activity of the renin-angiotensin-aldosterone system and stimulating the release of vasoactive hormones. Patients with CHF have diminished baroreflexes 53 and, as a result, a loss of normal responses to hemodynamic stress. 54-58 Various invasive and non-invasive techniques have been evaluated to study autonomic function. The analysis of HRV is an established non-invasive tool to assess autonomic function. Reduced HRV reflects the summation of the autonomic imbalances typically observed during CHF: excess sympathetic tone, parasympathetic withdrawal, and reduced baroreceptor sensitivity. 59,60

Autonomic function testing, based on cardiovascular reflexes,
another method to assess autonomic status; the use of several well defined ‘stress’ tests (the so called Ewing battery 61) provides information regarding sympathetic and parasympathetic function. Baroreflex function can be assessed invasively using drugs (phenylephrine [vasopressor] or nitroprusside [vasodepressor]) or non-invasively using a technique which directly measures muscle sympathetic nerve traffic (i.e. microneurography) 62 or a more recently introduced indirect technique which studies the relation between changes in arterial blood pressure and heart rate (i.e. baroreflex sensitivity). 63

Figure 4. Predicted survival curves based on initial measurement of plasma norepinephrine (from Cohn JN, N Engl J Med 1984)
AIMS OF THE THESIS

The first aim was to evaluate tools to monitor patients with CHF. In appendix 1, asymptomatic patients treated with cardiotoxic drugs for breast cancer were evaluated using HRV. It was hypothesized that early autonomic impairment occurs after treatment in the absence of left ventricular systolic dysfunction. In appendix 2, a new rapid natriuretic peptide assay (measuring BNP levels in whole blood) was evaluated to test the hypothesis that rapid measurement of BNP levels is comparable with conventional BNP measurement. In appendix 3, the technique of lower body negative pressure to simulate hypovolemia was used to test the hypothesis that neurohormonal and hemodynamic responses are impaired in the setting of CHF. In appendix 4, the relation between neurohormonal activation and the duration of concomitant atrial fibrillation in patients with CHF was evaluated.

The second aim was to study the progression and prognosis of CHF. In appendix 5, the concept was elaborated that plasma neurohormones are strongly associated with the prognosis in CHF. In appendix 6 the additional effect of atrial fibrillation in CHF patients was evaluated.

The third aim was to study drugs which are considered to have an effect on the autonomic and neurohormonal profile of patients with CHF. In appendix 7, the effect of mibefradil, a T-channel selective calcium channel blocker, on HRV parameters was studied in CHF. In appendix 8, autonomic function tests (Ewing battery) and HRV analysis were performed, before and during treatment with a β-blocker (metoprolol). Finally, in appendix 9, the effect of treatment with a selective dopa-mine agonist on plasma neurohormones, HRV and hemodynamics was evaluated.
References

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