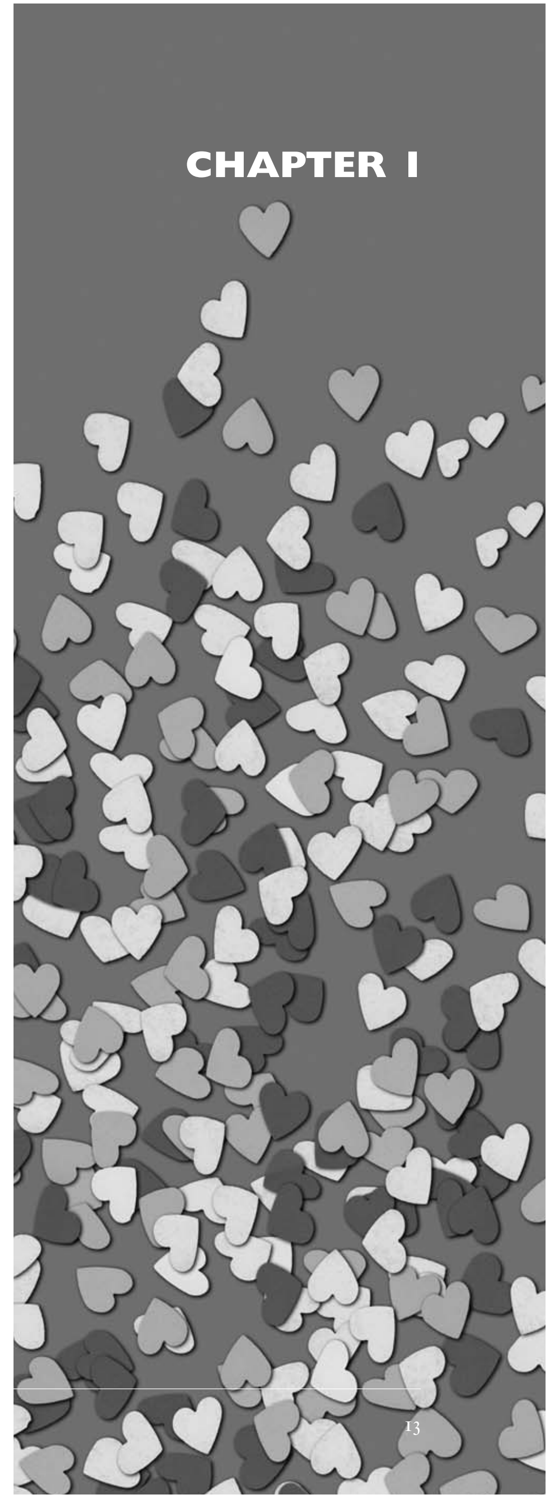
CHAPTER 1



INTRODUCTION

1.1 PREVALENCE AND PROGNOSIS OF HEART FAILURE

Heart failure (HF) was already described in antiquity. Around 400 BCE, Hippocrates gave a detailed description of the symptoms of this disease. He depicts one of his patients as follows: '[The patient] appears yellow; the whole body is edematous; the face is red; the mouth dry; he is thirsty; and when he eats, respiration quickens. In the same day at some times he may appear better while at others he is suffering acutely and seems on the verge of dying' (Internal Affections XXI)[44].

HF is a growing worldwide health problem. In the Netherlands, from 1980 to 1999, the annual hospitalization rate increased by 72%[56]. In the European population, the estimated prevalence of HF ranges from 0.4% up to 2%. The prevalence of HF increases rapidly with advancing age. The Framingham study reported an approximately 10 times higher occurrence of HF in the age group ≥ 80 years as in the age group 50–59 (91 versus 8 cases per 1000 persons)[36]. It is estimated that the world's population aged 60 and over will be three times higher in 2050 than in 2000 (2 billion). Hence, with a proportionally increasing older population, longevity partly accounts for this increasing occurrence of HF. Another factor that contributes to the rising prevalence of HF is the increasing post-infarction survival rate[54]: the occurrence of a myocardial infarction increases the risk for CHF 2–3 fold[74]. Also, it was found in patients ≥ 65 years in Canada, that 75% of this cohort developed HF within 5 years after their first myocardial infarction[24]. Furthermore, a high living standard with overweight and sedentary life style is also associated with HF[21,58]. According to the World Health Organization, in 2015, 2.3 billion people around the world will have a body mass index in the obese or overweight range. Consequently, this increase in obese people will add to the increasing prevalence of HF.

Despite the development of new therapies, the prognosis of HF remains poor[76]. Half of the HF patients dies within 4 years of the diagnosis, and less than half of the population with severe HF survives the first year after diagnosis[80]. This underscores the importance of the ongoing quest to improve current therapies and to develop new therapeutic modalities.

1.2 PATHOPHYSIOLOGY OF CHRONIC HEART FAILURE

An unifying definition of HF is lacking. There are, however, three items that are emphasized in most definitions, namely shortness of breath during rest and/or during exertion, fluid retention, and a functional or structural abnormality of the heart[21]. HF can occur acutely, e.g., in the setting of acute myocardial infarction, or it can be a chronic condition. A majority of research, including this thesis, focuses on chronic heart failure (CHF). Formerly, the abbreviation CHF stood for congestive HF; this usage has been abandoned, because adequate treatment keeps most of the HF patients out of the decompensated condition.

In 2001, the American Heart Association postulated a new approach to the classify HF[39]. Four stages were discerned in the pathogenesis and development of HF:

Stage A; At high risk for HF but without structural heart disease or symptoms of HF.
Stage B; Structural heart disease but without signs or symptoms of HF.
Stage C; Structural heart disease with prior or current symptoms of HF
Stage D; Refractory HF requiring specialized interventions.

With these stages, the Guidelines emphasize origin, development and progression of the disease, where 'pre'-stages A and B focus on the risk factors that predispose toward the development of actual HF (stages C and D). The mechanisms that cause structural heart disease (stage B) to develop into actual HF (stage C) are only partly known. Possibly, in HF developing on the basis of ischemia/infarction, increased apoptosis in the affected structures plays a major role, while it is hypertrophy and fibrosis in HF developing on the basis of increased afterload[42]. It is essential to realize that the before-mentioned processes originate and evolve in rest, a state where a beginning degradation of cardiac performance will not become manifest: in an early stage and only exercise would unmask a limitation in cardiac output.

It appears that chronic sympathoexcitation plays a pivotal role in the natural history of HF. Also, HF is associated with a weakened baroreflex[26]. Both sympathetic hyperactivity and lowered baroreflex sensitivity (BRS) are present in mild stage C HF[31] and the therapeutic effect of beta-blockade in patients with asymptomatic left ventricular systolic dysfunction (LVSD) suggests that chronic sympathoexcitation is also found in stage B heart failure[1]. As chronic sympathoexcitation leads to chronic activation of the renin-angiotensin-aldosteron system (RAAS) it implicates a generalized neurohumoral activation that is crucial for the remodeling of the heart as HF progresses[35], with enlargement due to increased filling pressure, and hypertrophy and fibrosis stimulated by increased levels of angiotensin and aldosteron[42].

What is the initial mechanism that causes sympathoexcitation in rest in emerging HF? The postulate of a diminished cardiac output that increases sympathetic outflow due to a decrease in baroreceptor firing rate caused by low blood pressure[62] is no longer a tenable hypothesis. First of all, cardiac output is not compromised at rest in the initial stage of emerging HF. Second, blood pressure is not lowered in asymptomatic patients. Third, if blood pressure would decrease, baroreflexes would reset to the prevailing new blood pressure value[16]. Fourth, in animal experiments with denervated baroreflex afferents, no signs of chronic sympathoexcitation were found, e.g., total peripheral resistance did not change[16]. Most likely, signals from the heart itself cause the sympathoexcitation.

It is reasonable to assume that in emerging HF localized areas in the heart come into existence in which increased mechanical stretch and/or metabolic stress/ischemia occur. Cardiac sympathetic afferents are then activated by mechanical stretch and by metabolites like potassium, hydrogen ion, adenosine, bradykinin and prostaglandins[63,83], resulting in elevation of sympathetic tone: the cardiac sympathetic afferent reflex (CSAR).

In normal hearts, CSAR is not excited at rest, but, in HF it is. Additionally, CSAR is enhanced in HF because of an increase in discharge intensity at the receptor level and also because of an increase in central reflex gain[51,86]. A schematic representation of the CSAR pathway is outlined in *Figure 1*. CSAR afferents project on the rostroventrolateral medulla (RVLM) and on the nucleus tractus solitarii (NTS). CSAR afferents activate sympathetic efferents at the level of the RVLM. At the level of the NTS, CSAR afferents activate interneurons[71,86]. These interneurons release the neuromodulator gamma-aminobutyric acid (GABA) that inhibits the barosensitive NTS neurons[87]. As a result CSAR increases sympathetic outflow and reduces BRS.

Hence, permanent CSAR activation might well be the initial cause of the chronic sympathoexcitation in HF. As HF progresses, and due to changes in blood composition due to the permanent neurohumoral activation, skeletal muscle becomes involved. Due to several structural and functional changes, mataboreceptors, normally only stimulated during exercise, become also active at rest. This permanent stimulation of the peripheral chemoreflex causes additional sympathoexcitation[89].

As patients with the highest sympathetic activation and patients with the lowest BRS have the poorest survival[4,10], lowering CSAR activity, sympathoexcitation and plasma catecholamine concentrations, and increasing BRS, seem logical therapeutic goals in emerging and overt HF.

1.3 FITNESS

Fitness is a broad term. According to the Dutch Van Dale dictionary, fitness means being physically in good shape. Oftentimes, the ability to cope with stress is included in the definition of the word. In this thesis we focus on two different aspects of fitness that are specifically relevant in CHF: exercise capacity and autonomic functioning.

1.3.1 Fitness and exercise capacity in CHF

In CHF patients exercise capacity is decreased, frequently to such an extent that participation in several daily life activities becomes impossible. The degree of exercise intolerance in CHF is paralleled by an increased mortality[18], moreover, several studies suggest that increasing exercise capacity in CHF improves prognosis[68,73,77]. Therefore, improving exercise capacity is one of the major issues in CHF-related treatment. Part of this thesis concentrates on the effect of therapeutic interventions on fitness in the context of exercise capacity, focusing on changes in fitness-related cardiopulmonary exercise variables discussed below.

Clinically, the maximal oxygen uptake ($\dot{V}O_{2\,max}$) is the most frequently used measure of exercise capacity. $\dot{V}O_{2\,max}$ is an objective parameter, being defined as the point at which oxygen uptake reaches a plateau despite continuing exercise and increasing workload[82] (see *Figure 2*). Unfortunately, such a plateau is often difficult to perceive[57], and in symptom-limited exercise tests, as performed in CHF, the plateau is often not attained[81] (see *Figure 2*), hence, peak oxygen uptake ($\dot{V}O_{2\,peak}$) is assessed instead. By its nature, $\dot{V}O_{2\,peak}$ is in practice strongly influenced by the motivation of the patient, the selected exercise protocol and the tester's subjective choice of the test endpoint[5,79]. Consequently, $\dot{V}O_{2\,peak}$ is more a subjective parameter.

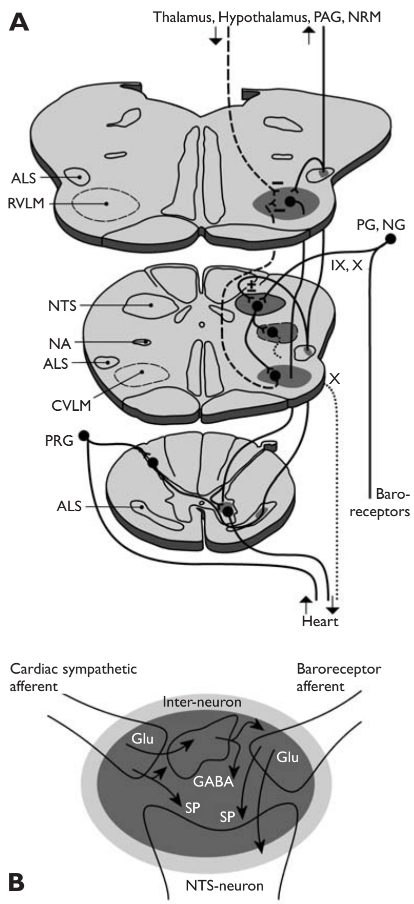


Figure 1. *Neural pathways involved in sympathoexcitation and baroreflex inhibition by cardiac sympathetic afferents.*
Gademan et al. Am J Physiol *2008.*
Panel A: sacral and thoracic spinal, and caudal and rostral medullar sections;
panel B: NTS details (based on[71]). ALS = anterolateral (spinothalamic) system; CVLM = caudal ventrolateral medulla; GABA = inhibiting neuromodulator gamma-aminobutyric acid; Glu = excitatory neurotransmitter L-glutamate; NA = nucleus ambiguus; NG = nodose ganglion; NRM = nucleus raphe magnus; NTS = nucleus tractus solitarius; PAG = periaquaductal grey; PG = petrosal ganglion; PRG = posterior (dorsal) root ganglion; RVLM = rostral ventrolateral medulla; SP = excitatory neuromodulator substance P; IX = 9th cranial (glossopharyngeal) nerve; X = 10th cranial (vagus) nerve. Dark gray spots: involved areas. Inhibiting neurons at the level of the brainstem: gray, dashed; sympathetic efferents: gray, continuous; parasympathetic efferents: gray, dotted.

More objective measures of exercise capacity than $\dot{V}O_{2\,peak}$ can be assessed by submaximal exercise testing (or by the submaximal part of a symptom limited exercise test), such as $\dot{V}E/\dot{V}CO_2$ slope, the oxygen uptake efficiency slope (OUES) and the oxygen uptake-work rate relation ($\Delta\dot{V}O_2/\Delta W$).

The $\dot{V}E/\dot{V}CO_2$ slope is an exercise testing parameter with high prognostic value in CHF[13,18]. It can be obtained by linear regression analysis of the relation between minute ventilation ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$) during an incremental exercise test (see *Figure 3*). It reflects the ventilatory response to exercise, *i.e.*, the slope reflects the gain of the chemoreflex that triggers ventilation in response to PCO_2 changes in the blood. As a consequence of overactive chemoreceptors, the $\dot{V}E/\dot{V}CO_2$ slope is increased in CHF. Normal values of the $\dot{V}E/\dot{V}CO_2$ slope are between 20 and 30; in CHF patients it can reach values as high as 80[67].

In 1996 Baba et al.[7] introduced OUES as an objective and reproducible measure of exercise capacity[8,37,85] (see *Figure 4*). The OUES is determined by regressing oxygen uptake against the logarithm of total ventilation during an incremental exercise test. It describes the efficiency by which oxygen can be extracted from the ambient air. In CHF patients it was shown that among other exercise-test derived parameters ($\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$ slope and ventilatory anaerobic threshold) OUES had the strongest prognostic value; OUES was also the only exercise variable with independent prognostic value[18].

Another measure of exercise capacity is $\Delta\dot{V}O_2/\Delta W$, which can be used as a supplemental index to the other exercise testing variables to more precisely assess exercise capacity. $\Delta\dot{V}O_2/\Delta W$ describes the amount of oxygen that is utilized in relation to the amount of external work performed (see *Figure 5*); $\Delta\dot{V}O_2/\Delta W$ on itself, also has important prognostic power in CHF[46]. $\Delta\dot{V}O_2/\Delta W$ is often reduced in CHF, and

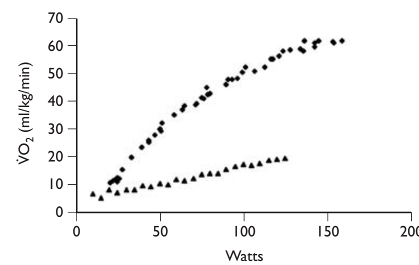


Figure 2. *Peak oxygen uptake*
Peak oxygen uptake of a healthy male (◆, age 48) and a male chronic heart failure patient (▲, age 48). The oxygen uptake of the healthy male reaches a plateau, the oxygen uptake of the chronic heart failure patient does not reach a plateau.

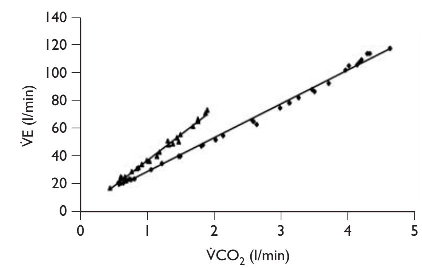


Figure 3. $\dot{V}E/\dot{V}CO_2$ *slope*
◆: *$\dot{V}E/\dot{V}CO_2$ slope of a healthy male (age 48), $\dot{V}E/\dot{V}CO_2$ slope = 24;*
▲: *$\dot{V}E/\dot{V}CO_2$ slope of a male chronic heart failure patient (age 53), $\dot{V}E/\dot{V}CO_2$ slope = 37.*

the reduction in $\Delta\dot{v}o_2/\Delta w$ reflects the severity of CHF[40,78]. However, patients with mild CHF may have relatively normal $\Delta\dot{v}o_2/\Delta w$ values[78].

1.3.2 Fitness and autonomic functioning in CHF

Discussing autonomic functioning in the context of fitness is less evident than discussing exercise capacity. However, exercise capacity and autonomic functioning in CHF are closely related[41,52], as physical training improves both exercise capacity and autonomic functioning, the latter manifesting, e.g., as a decrease in neurohumoral activation and an increase in BRS[27]. Major part of this thesis is concerned with improvement of autonomic functioning in CHF, mainly focusing on the arterial baroreflex.

The arterial baroreflex buffers blood pressure and it prevents wide short-term fluctuations of arterial blood pressure. Baroreceptors are stretch-sensitive receptors located in the aortic wall, the wall of the pulmonary artery, and the carotid sinuses. Every blood pressure pulsation elicits an afferent baroreceptor burst, of which the intensity depends on the systolic blood pressure (SBP) of the given heart beat relative to the average blood pressure level. Hence, when the SBP of the given heart beat is relatively low, the burst intensity of the baroreceptor will also be low, and when the SBP of the given heart beat is relatively high, the burst intensity of the baroreceptor will also be high. The afferent baroreceptor burst constitutes neural information for the vasomotor centre in the medulla oblongata[62]. Here, the efferent reflex output is generated, both in the form of a vagal burst (more intense with a higher blood pressure pulsation) and in the form of a brief episode of sympathoinhibition (the degree of inhibition increasing with blood pressure).

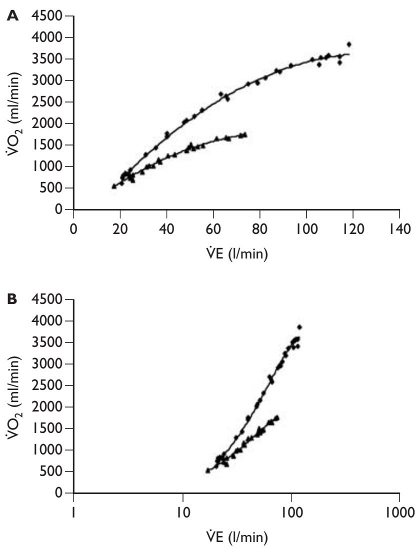


Figure 4. *The oxygen uptake efficiency slope Panel A: The relationship between oxygen uptake and minute ventilation during exercise in a 53-year old chronic heart failure patient (▲) and in a healthy male (age 48, ◆).*
Panel B: The relation plotted on a logarhytmic scale. The slope of panel B represents the oxygen uptake efficiency.

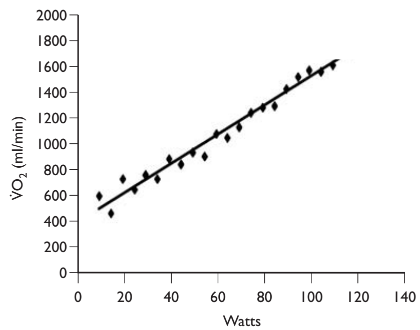


Figure 5. *Oxygen uptake kinetics ($\Delta\dot{v}o_2/\Delta w$) The oxygen uptake – work rate relation of a 48 year old chronic heart failure patient. This relation describes how much oxygen is consumed in relation to the quantity of external work performed.*

Baroreflex vigor is usually characterized in terms of the extent of bradycardia that occurs when blood pressure increases, and is indicated by BRS. BRS is expressed as the increase of the interval between heart beats (in ms) per mmHg systolic blood pressure rise and is usually determined during rest. Lowered BRS in CHF parallels deterioration of clinical and hemodynamic status and is strongly associated with poor survival[48,55].

1.4 TREATMENT OF HEART FAILURE

A broad therapeutic spectrum is used in CHF. The cornerstone of CHF management is pharmacological therapy, where each patient is to be submitted to an individualized combination of the following medications to achieve an optimal treatment effect: angiotensin-converting (ACE) inhibitors, diuretics, beta-adrenoreceptor antagonists, aldosterone receptor antagonists, angiotensin receptor antagonists, cardiac glycosides, vasodilator agents (nitrates/hydralazine), positive inotropic agents, anticoagulation and antiarrhytmic agents. Treatment with this pharmacological regimen interferes at various levels with the process of neurohumoral activation, thus reducing the detrimental influences of this process to a certain extent[21].

Besides pharmacological therapy, surgical treatment is an option for part of the CHF patients. Common surgical interventions are: coronary revascularization, valvular surgery and surgical remodeling of the left ventricle. For patients with end-stage drug refractory CHF, cardiac transplantation may be the last option. Supplementary to pharmacological therapy and/or surgical intervention, device therapy (implantable cardiovertor defibrillator and/or biventricular pacemaker, *Figure 6*) has been implemented in the last decade as therapy for patients with both drug refractory CHF and left ventricular dysfunction.

Another important part of treatment of CHF is self-care management. Self-care can be defined as actions by the patient intended at maintaining physical stability, avoidance of behavior that can worsen the condition, and recognition of the early symptoms of deterioration[43]. One of the aspects of self-care management is being physically active. In practice, a limited period of exercise training/rehabilitation is often prescribed/advised following a cardiovascular event, an episode of decompensation or to recover from surgical interventions. However, exercise training could be a more beneficial therapy if it is incorporated in daily life and not only used occasionally in situations as mentioned above.

In this thesis we focus on the fitness-related effects of two non-pharmacological treatment modalities within the scope of the cardiologist, namely exercise training and biventricular pacing.

1.5 MECHANISMS AND EFFECTS OF EXERCISE TRAINING

In the past, patients with CHF were advised to avoid exertion, for fear of worsening cardiac function due to myocardial stress[38]. In the late

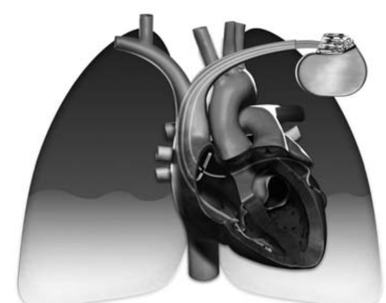


Figure 6. *A biventricular pacing device, the leads are positioned in the right atrium, the right ventricle (usually the apex) and a postero-lateral vein (through the coronary sinus).*

1970s and early 1980s the first studies appeared reporting that exercise training was safe in patients with CHF[15,50]. At present, it is clear that exercise training is not only safe but also beneficial in CHF. Exercise training lessens dyspnea and fatigue[34,53], improves quality of life, improves New York Heart Association (NYHA) class[6,9,20,61,65,84], decreases morbidity and, likely, also mortality[19,68,73,77]. Currently, European and American guidelines[21,38] recommend exercise training in addition to pharmacotherapy.

Beneficial effects of exercise training in CHF have been documented at various functional and structural levels. Several peripheral muscular adaptations occur under the influence of exercise training, for instance, increased capillary density, blood flow, mitochondrial volume density, fibre size, slow twitch fibres and decreased lactic acidosis and vascular resistance[22,30,33,34,45,69]. Although the ELVD-CHF trial[29] reported a slightly increased left ventricular ejection fraction, most studies report hardly any change in this variable[70]. The generally observed exercise-training induced increase in $\dot{V}O_{2\,peak}$[73] is presumably mainly to be attributed to an increase in peak heart rate, an increase in stroke volume during exercise and to peripheral muscular adaptations. Other cardiopulmonary exercise testing variables than $\dot{V}O_{2\,peak}$, that are increased by exercise training in CHF are the $\dot{V}E/\dot{V}CO_2$ slope, ventilatory anaerobic threshold and workload. The effect of exercise training in CHF on OUES and $\Delta\dot{V}O_2/\Delta W$ has not been elucidated yet.

In addition to these effects, exercise training in CHF also reduces autonomic derangement and neurohumoral excitation at rest[27]; exercise training decreases sympathetic outflow and increases BRS in CHF. However, the mechanism that mediates the normalization of the neurohumoral activation and autonomic derangement by exercise training has not yet been identified. Pinpointing the key elements of an exercise program that are responsible to achieve an autonomic training effect would allow for the design of training programs specific for CHF patients, with maximal efficacy at minimal work loads that meet the limited exercise tolerance.

Ergoreceptor activity stemming from working muscle may be a key factor in the exercise-induced increase in BRS at rest. On their way to the thalamus, the neural fibres conveying such ergoreceptor information project to several structures, such as the NTS[17]. During exercise, these projections release substance P at the NTS[72]. Substance P enhances the baroreflex[66] by modulating the transmission of the baroreceptive afferents to the NTS neurons. We assume that baroreflex enhancement after exercise materializes in the NTS in the form of an elevated substance P level that outlasts the actual exercise period[88]. The enduring production of substance P by baroreceptor afferents[71] would make such a sustained effect even more likely. We suppose that this effect lasts for more than 24 hours, thus facilitating a lasting cumulative training effect that can be achieved by daily stimulation. Substance P has long-lasting effects (>24 hours) on the modulation of neural activity in other systems, e.g., in the spinal cord[64]. It is however not known if substance P has these long-lasting effects in the NTS. In any case, the consequence of this scenario would be that baroreflex training effects could also be attained by exercise-mimicking somatosensory stimulation alone, without actual accompanying exercise.

1.6 EFFECTS/MECHANISMS OF BIVENTRICULAR PACING ON FITNESS

Cardiac resynchronization therapy (CRT) is a relatively new therapy in CHF; the first case report of a patient who received CRT appeared in 1994[12]. Currently, it is known that CRT improves mortality, symptoms, quality of life and NYHA class[2,14]. As a result of these successful outcomes, CRT is nowadays an established therapy in CHF.

Improvement of the mechanical activation pattern of the left ventricle is the primary working mechanism of CRT[49]. CRT induces early excitation of the region which is else late activated due to delayed intrinsic conduction, hence, biventricular pacing synchronizes the activation of the left ventricular free wall and the intraventricular septum and improves mechanical contractility and mitral regurgitation. Moreover, Nelson et al.[59] found that CRT enhanced systolic function with modestly diminished energy cost, which is probably explained by lowering of lateral wall stress.

As CRT enhances systolic function and improves myocardial efficiency in CHF, it is not surprising that CRT also improves exercise capacity, since oxygen uptake depends on cardiac output[67]. In the MIRACLE trial it was shown that CRT improved $\dot{V}O_{2\,peak}$, as well as submaximal exercise capacity, measured by the six minute walk test[2].

In addition to the beneficial clinical effects of CRT on fitness in the context of exercise capacity, CRT also has a positive impact on autonomic functioning in CHF. CRT has been proven to reduce sympathetic nerve activity, BNP, ET-1 and norepinephrine and to increase heart rate variability after six months[3,11,23,25,32,47,60,75]. A plausible and clinically relevant explanation for these observations would be that CRT reduces metabolic and mechanical stress in affected ventricular muscle, thus reversing CSAR activation and sympathetic outflow. However, direct proof of this CRT working mechanism is difficult to obtain, as CSAR afferent activity cannot be measured in humans.

1.7 AIMS AND OUTLINE OF THIS THESIS

Aim of this thesis is to study the effects of exercise training and of biventricular pacing on fitness-related cardiopulmonary exercise testing variables and on BRS in the setting of CHF. Also, we address the underlying effect mechanisms.

In *Chapter 2* we review the effects of exercise training on neurohumoral excitation and autonomic derangement at rest.

In *Chapter 3* we address, in a modeling study, a number of issues that are relevant for the interpretation of BRS. By means of computer simulations we investigate the link between the well known phenomena of blood pressure resonance (the Mayer waves) on one hand, and blood pressure buffering (possibly the most essential function of the baroreflex) on the other hand.

In *Chapter 4* we probe the hypothesis that sole exercise-associated somatosensory input to the brainstem is a training stimulus for the autonomic nervous system. We compare in stable untrained CHF patients the effect of transcutaneous electrical nerve stimulation (TENS) with the effects of bicycle exercise training. BRS was used as an outcome measure of autonomic functioning. To mimic exercise-associated somatosensory ergoreceptor stimulation by TENS, we applied periodic (2/s, marching pace) burst stimulation to both feet.

Chapters 5 and *6* are devoted to the effect of exercise training on fitness in the context of exercise capacity. We studied the effect of exercise training in CHF patients on the OUES (chapter 5) and on oxygen uptake - work relation (chapter 6). In contrast to the $\dot{V}O_{2\,max}$, OUES and $\Delta\dot{V}O_2/\Delta W$ are independent of the maximally attained exercise intensity. Therefore both are very convenient and reliable measures of exercise capacity in CHF.

In *Chapters 7* and *8* we describe the effect of biventricular pacing on the arterial baroreflex. Since CSAR afferent firing is known to decrease BRS[28,87], CRT-induced CSAR deactivation should be accompanied by a BRS increase.

In *Chapter 7* we describe the acute effect of biventricular pacing on the arterial baroreflex. As no other studies have yet found an acute effect of CRT on autonomic fitness in the form of an increase in BRS, this study may reveal a new indication for the working mechanisms of biventricular pacing.

In *Chapter 8* we investigate if the acute response in BRS after institution of CRT has predictive value for mid-term response.

REFERENCE LIST

1. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. *N Engl J Med* 1992;327:685-691.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
3. Adamson PB, Kleckner KJ, van Hout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;108:266-269.
4. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation* 2003;107:1278-1283.
5. Andreacci JL, LeMura LM, Cohen SL, Urbansky EA, Chelland SA, Von Duvillard SP. The effects of frequency of encouragement on performance during maximal exercise testing. *J Sports Sci* 2002;20:345-352.
6. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail* 2005;7:411-417.
7. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996;28:1567-1572.
8. Baba R, Tsuyuki K, Kimura Y, Ninomiya K, Aihara M, Ebine K et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol* 1999;80:397-401.
9. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999;99:1173-1182.
10. Benedict CR, Shelton B, Johnstone DE, Francis G, Greenberg B, Konstam M et al. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. SOLVD Investigators. Circulation 1996;94:690-697.
11. Burri H, Sunthorn H, Somsen A, Fleury E, Stettler C, Shah D et al. Improvement in cardiac sympathetic nerve activity in responders to resynchronization therapy. *Europace* 2008;10:374-378.
12. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L et al. Four chamber pacing in dilated cardiomyopathy. *Pacing Clin Electrophysiol* 1994;17:1974-1979.
13. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997;29:1585-1590.
14. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.
15. Conn EH, Williams RS, Wallace AG. Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. *Am J Cardiol* 1982;49:296-300.
16. Cowley AW, Jr., Liard JF, Guyton AC. Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. *Circ Res* 1973;32:564-576.
17. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3:655-666.
18. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* 2006;27:684-690.
19. De Sutter JHAJ, Ascoop AK, van de Veire N, De Winter O, Salhi B, De Backer G. Exercise training results in a significant reduction of mortality and morbidity in heart failure patients on optimal medical treatment. *Eur Heart J* 2005;Abstract 370.
20. Delagardelle C, Feiereisen P, Autier P, Shita R, Krecke R, Beissel J. Strength/endurance training versus endurance training in congestive heart failure. *Med Sci Sports Exerc* 2002;34:1868-1872.
21. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388-2442.
22. Dubach P, Myers J, Dziekan G, Goebbels U, Reinhart W, Muller P et al. Effect of high intensity exercise training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol* 1997;29:1591-1598.
23. Erol-Yilmaz A, Verberne HJ, Schrama TA, Hrudova J, De Winter RJ, Eck-Smit BL et al. Cardiac resynchronization induces favorable neurohumoral changes. *Pacing Clin Electrophysiol* 2005;28:304-310.
24. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009;53:13-20.
25. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere

MT, Prentice J et al. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. *J Am Coll Cardiol* 2005;46:1875–1882.
26. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. *Heart* 2004;90:1248–1255.
27. Gademan MG, Swenne CA, Verwey HF, van der Laarse A, Maan AC, van de Vooren H et al. Effect of exercise training on autonomic derangement and neurohumoral activation in chronic heart failure. *J Card Fail* 2007;13:294–303.
28. Gao L, Schultz HD, Patel KP, Zucker IH, Wang W. Augmented input from cardiac sympathetic afferents inhibits baroreflex in rats with heart failure. *Hypertension* 2005;45:1173–1181.
29. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation* 2003;108:554–559.
30. Gordon A, Tyni-Lenne R, Persson H, Kaijser L, Hultman E, Sylven C. Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiol* 1996;19:568–574.
31. Grassi G, Seravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation* 1995;92:3206–3211.
32. Grassi G, Vincenti A, Brambilla R, Trevano FQ, Dell'Oro R, Ciro A et al. Sustained sympathoinhibitory effects of cardiac resynchronization therapy in severe heart failure. *Hypertension* 2004;44:727–731.
33. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol* 1997;29:1067–1073.
34. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA* 2000;283:3095–3101.
35. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation* 2003;107:984–991.
36. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22:6A–13A.
37. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000;36:194–201.
38. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154–e235.
39. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101–2113.
40. Itoh H, Taniguchi K, Koike A, Doi M. Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation* 1990;81:II31–II37.
41. Itoh K, Osada N, Inoue K, Samejima H, Seki A, Omiya K et al. Relationship between exercise intolerance and levels of neurohormonal factors and proinflammatory cytokines in patients with stable chronic heart failure. *Int Heart J* 2005;46:1049–1059.
42. Izzo JL, Gradman AH. Mechanisms and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure. *Med Clin North Am* 2004;88:1257–1271.
43. Jaarsma T, Stromberg A, Martensson J, Dracup K. Development and testing of the European Heart Failure Self-Care Behaviour Scale. *Eur J Heart Fail* 2003;5:363–370.
44. Katz AM, Katz PB. Diseases of the heart in the works of Hippocrates. *Br Heart J* 1962;24:257–264.
45. Keteyian SJ, Brawner CA, Schairer JR, Levine TB, Levine AB, Rogers FJ et al. Effects of exercise training on chronotropic incompetence in patients with heart failure. *Am Heart J* 1999;138:233–240.
46. Koike A, Itoh H, Kato M, Sawada H, Aizawa T, Fu LT et al. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest* 2002;121:1581–1588.
47. Kubanek M, Malek I, Bytesnik J, Fridl P, Riedlbauchova L, Karasova L et al. Decrease in plasma B-type natriuretic peptide early after initiation of cardiac resynchronization therapy predicts clinical improvement at 12 months. *Eur J Heart Fail* 2006;8:832–840.
48. La Rovere MT, Pinna GD, Maestri R, Robbi E, Caporotondi A, Guazzotti G et al. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. *J Am Coll Cardiol* 2009;53:193–199.
49. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002;39:194–201.
50. Lee AP, Ice R, Blessey R, Sanmarco ME. Long-term effects of physical training on coronary patients with impaired ventricular function. *Circulation* 1979;60:1519–1526.
51. Ma R, Zucker IH, Wang W. Central gain of the cardiac sympathetic afferent reflex in dogs with heart failure. *Am J Physiol* 1997;273:H2664–H2671.
52. Maeder M, Wolber T, Rickli H, Myers J, Hack D, Riesen W et al. B-type natriuretic peptide kinetics and cardiopulmonary exercise testing in heart failure. *Int J Cardiol* 2007;120:391–398.
53. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am Heart J* 2002;144:23–30.
54. McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart* 2000;83:596–602.
55. Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O et al. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997;96:3450–3458.
56. Mosterd WL, Rossier PF, Balk AH, Geijer RM, De Graeff PA, Jansen RW et al. Multidisciplinaire richtlijn Chronisch Hartfalen. 2002. van Zuiden, Alphen aan den Rijn.
57. Myers J, Walsh D, Buchanan N, Froelicher VF. Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? *Chest* 1989;96:1312–1316.
58. Najafi F, Jamrozik K, Dobson AJ. Understanding the 'epidemic of heart failure': a systematic review of trends in determinants of heart failure. *Eur J Heart Fail* 2009.
59. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;102:3053–3059.
60. Nishioka SA, Martinelli FM, Brandao SC, Giorgi MC, Vieira ML, Costa R et al. Cardiac sympathetic activity pre and post resynchronization therapy evaluated by 123I-MIBG myocardial scintigraphy. *J Nucl Cardiol* 2007;14:852–859.
61. Oka RK, De Marco T, Haskell WL, Botvinick E, Dae MW, Bolen K et al. Impact of a home-based walking and resistance training program on quality of life in patients with heart failure. *Am J Cardiol* 2000;85:365–369.
62. Opie LH. Heart Phyiology; from cell to circulation. 2004. Lippincott Williams & Wilkins, Philadelphia.
63. Pan HL, Longhurst JC, Eisenach JC, Chen SR. Role of protons in activation of cardiac sympathetic C-fibre afferents during ischaemia in cats. *J Physiol* 1999;518 (Pt 3):857–866.
64. Parker D, Grillner S. Long-lasting substance-P-mediated modulation of NMDA-induced rhythmic activity in the lamprey locomotor network involves separate RNA- and protein-synthesis-dependent stages. *Eur J Neurosci* 1999;11:1515–1522.
65. Parnell MM, Holst DP, Kaye DM. Exercise training increases arterial compliance in patients with congestive heart failure. *Clin Sci* (Lond) 2002;102:1–7.
66. Petty MA, Reid JL. Opiate analogs, substance P, and baroreceptor reflexes in the rabbit. *Hypertension* 1981;3:I142–I147.
67. Piepoli MF, Corra U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006;13:150–164.
68. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189.
69. Piepoli MF, Scott AC, Capucci A, Coats AJ. Skeletal muscle training in chronic heart failure. *Acta Physiol Scand* 2001;171:295–303.
70. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation* 2003;107:1210–1225.
71. Potts JT. Neural circuits controlling cardiorespiratory responses: baroreceptor and somatic afferents in the nucleus tractus solitarius. *Clin Exp Pharmacol Physiol* 2002;29:103–111.
72. Potts JT, Fuchs IE, Li J, Leshnower B, Mitchell JH. Skeletal muscle afferent fibres release substance P in the nucleus tractus solitarii of anaesthetized cats. *J Physiol* 1999;514 (Pt 3):829–841.
73. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;CD003331.
74. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* 2008;117:2544–2565.
75. Seifert M, Schlegl M, Hoersch W, Fleck E, Doelger A, Stockburger M et al. Functional capacity and changes in the neurohormonal and cytokine status after long-term CRT in heart failure patients. *Int J Cardiol* 2007;121:68–73.
76. Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women

with heart failure of ischaemic and non-ischaemic origin: data for the period 1987-2003 from the Swedish Hospital Discharge Registry. *Eur Heart J* 2008.
77. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004;116:693-706.
78. Solal AC, Chabernaud JM, Gourgon R. Comparison of oxygen uptake during bicycle exercise in patients with chronic heart failure and in normal subjects. *J Am Coll Cardiol* 1990;16:80-85.
79. St Clair GA, Lambert MI, Hawley JA, Broomhead SA, Noakes TD. Measurement of maximal oxygen uptake from two different laboratory protocols in runners and squash players. *Med Sci Sports Exerc* 1999;31:1226-1229.
80. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:1115-1140.
81. Swedberg K, Gundersen T. The role of exercise testing in heart failure. *J Cardiovasc Pharmacol* 1993;22 Suppl 9:S13-S17.
82. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardio-respiratory performance. *J Appl Physiol* 1955;8:73-80.
83. Tjen ALS, Pan HL, Longhurst JC. Endogenous bradykinin activates ischaemically sensitive cardiac visceral afferents through kinin B2 receptors in cats. *J Physiol* 1998;510 (Pt 2):633-641.
84. Tyni-Lenne R, Dencker K, Gordon A, Jansson E, Sylven C. Comprehensive local muscle training increases aerobic working capacity and quality of life and decreases neurohormonal activation in patients with chronic heart failure. *Eur J Heart Fail* 2001;3:47-52.
85. van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J* 2005;149:175-180.
86. Wang W, Schultz HD, Ma R. Cardiac sympathetic afferent sensitivity is enhanced in heart failure. *Am J Physiol* 1999;277:H812-H817.
87. Wang WZ, Gao L, Pan YX, Zucker IH, Wang W. Differential effects of cardiac sympathetic afferent stimulation on neurons in the nucleus tractus solitarius. *Neurosci Lett* 2006;409:146-150.
88. Williams CA, Reifsteck A, Hampton TA, Fry B. Substance P release in the feline nucleus tractus solitarius during ergoreceptor but not baroreceptor afferent signaling. *Brain Res* 2002;944:19-31.
89. Zucker IH, Wang W, Pliquett RU, Liu JL, Patel KP. The regulation of sympathetic outflow in heart failure. The roles of angiotensin II, nitric oxide, and exercise training. *Ann N Y Acad Sci* 2001;940:431-443.