Fitness in chronic heart failure : effects of exercise training and of biventricular pacing

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EFFECTS OF EXERCISE TRAINING AND OF
BIVENTRICULAR PACING

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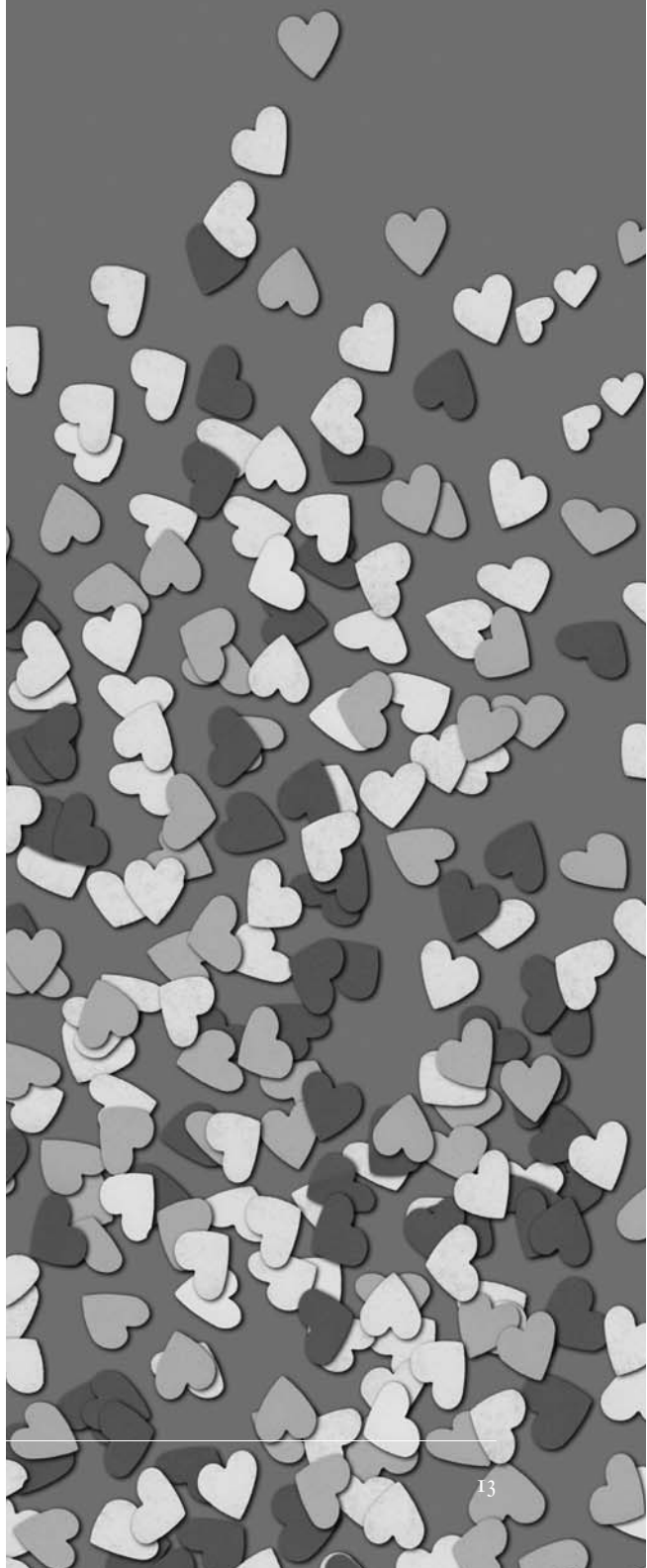
'Enkel met het hart kan men goed zien,
het essentiële is onzichtbaar voor de ogen'

(ANTOINE DE SAINT-EXUPÉRY)

Aan Jens

CONTENTS

CHAPTER I



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 RLVM. 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.

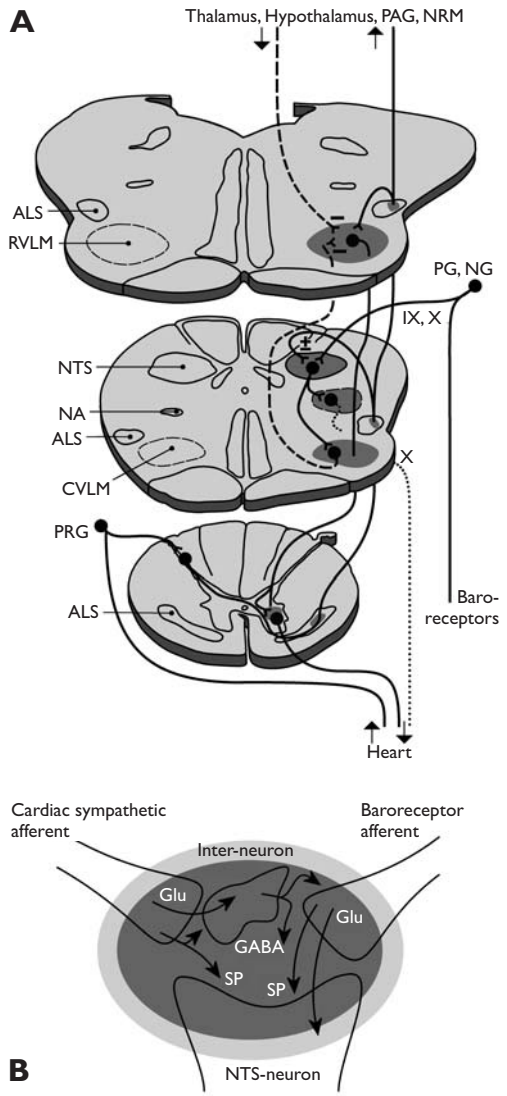


Figure 1. *Neural pathways involved in sympathoexcitation and baroreflex inhibition by cardiac sympathetic afferents.*
Gademan et al. Am J Physiol *2008.*
Panel A: sacral and thoracic spinal, and caudal and rostral medullar sections;
panel B: NTS *details (based on*[71]*).* ALS *= anterolateral (spinothalamic) 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.*

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].

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 ($\Delta\dot{V}O_2/\Delta w$).

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

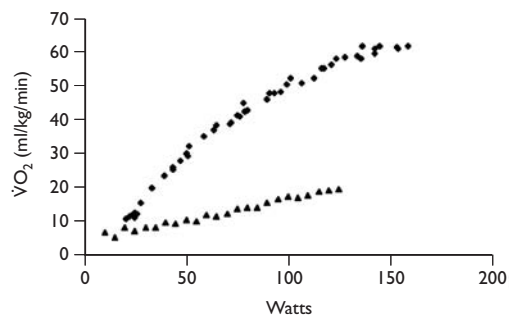


Figure 2. *Peak oxygen uptake*
Peak oxygen uptake of a healthy male (◆, age 48) and a male chronic heart failure patient (▲, age 48). The oxygen uptake of the healthy male reaches a plateau, the oxygen uptake of the chronic heart failure patient does not reach a plateau.

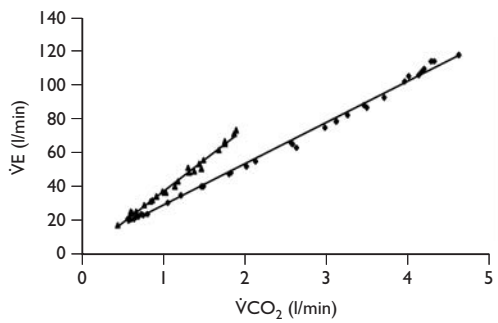


Figure 3. $\dot{V}E/\dot{V}CO_2$ *slope*
◆: $\dot{V}E/\dot{V}CO_2$ *slope of a healthy male (age 48),* $\dot{V}E/\dot{V}CO_2$ *slope = 24;*
▲: $\dot{V}E/\dot{V}CO_2$ *slope of a male chronic heart failure patient (age 53),* $\dot{V}E/\dot{V}CO_2$ *slope = 37.*

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).

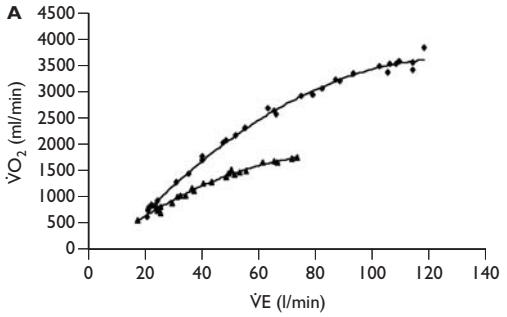


Figure 4. *The oxygen uptake efficiency slope*
Panel A: The relationship between oxygen uptake and minute ventilation during exercise in a 53-year old chronic heart failure patient (▲) and in a healthy male (age 48, ◆).
Panel B: The relation plotted on a logarhytmic scale. The slope of panel B represents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

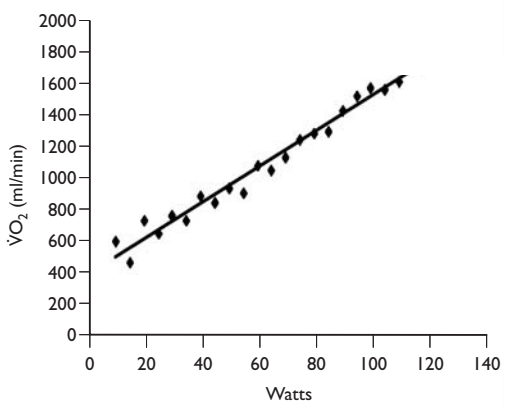


Figure 5. *Oxygen uptake kinetics ($\Delta\dot{V}O_2/\Delta w$)*
The oxygen uptake – work rate relation of a 48 year old chronic heart failure patient. This relation describes how much oxygen is consumed in relation to the quantity of external work performed.

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

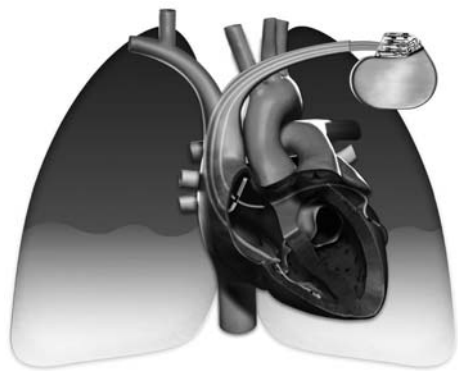


Figure 6. *A biventricular pacing device, the leads are positioned in the right atrium, the right ventricle (usually the apex) and a postero-lateral vein (through the coronary sinus).*

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.

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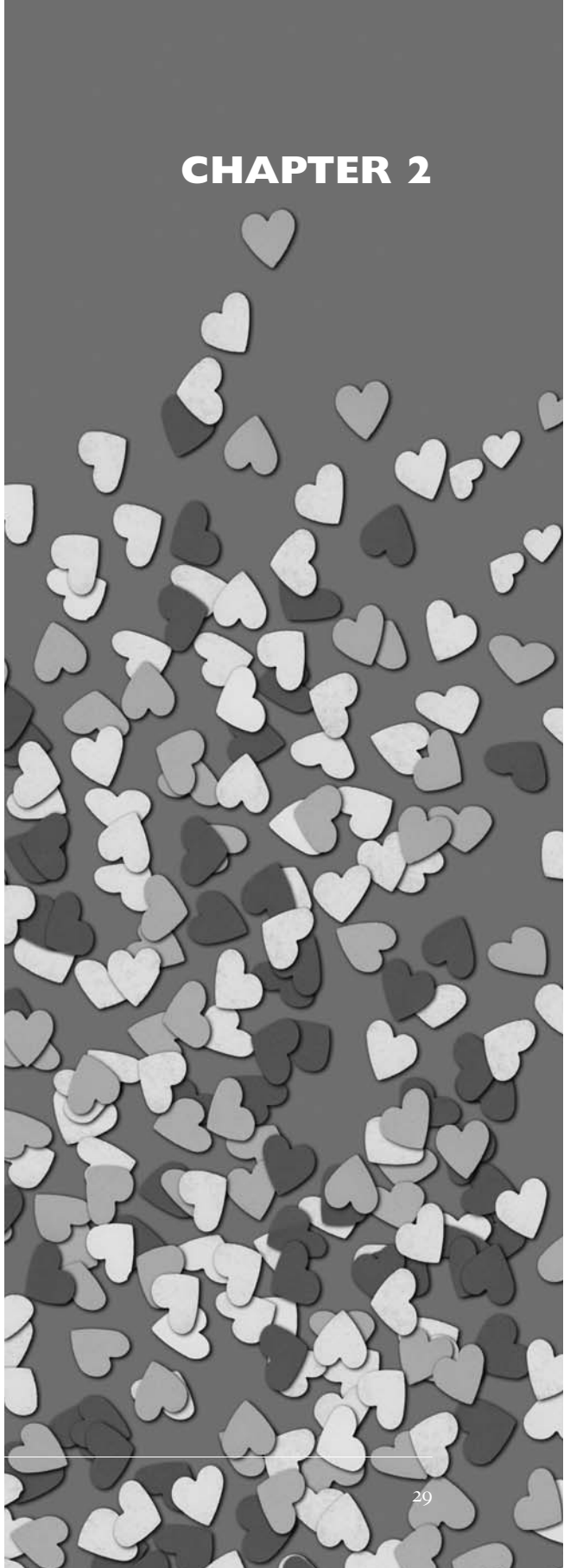
CHAPTER 2



EFFECT OF EXERCISE TRAINING ON AUTONOMIC DERANGEMENT AND NEUROHUMORAL ACTIVATION IN CHRONIC HEART FAILURE

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ABSTRACT

Background. In chronic heart failure (CHF), persistent autonomic derangement and neurohumoral activation cause structural end-organ damage, decrease exercise capacity and reduce quality of life. Beneficial effects of pharmacotherapy and of exercise training in CHF have been documented at various functional and structural levels. However, pharmacological treatment can not yet reduce autonomic derangement and neurohumoral activation in CHF to a minimum. Various studies suggest that exercise training is effective in this respect.
Results. After reviewing the available evidence we conclude that exercise training increases baroreflex sensitivity and heart rate variability, and reduces sympathetic outflow, plasma levels of catecholamines, angiotensin II, vasopressin and brain natriuretic peptides at rest.
Conclusions. Exercise training has direct and reflex sympathoinhibitory beneficial effects in CHF. The mechanism by which exercise training normalizes autonomic derangement and neurohumoral activation is to elucidate for further development of CHF-related training programs aimed at maximizing efficacy while minimizing workload.

INTRODUCTION

Chronic heart failure (CHF) is associated with autonomic derangement, notably, permanent sympathoexcition and arterial baroreflex sensitivity (BRS) weakening[29]. Autonomic derangement is already present in mild CHF[36], and is likely to be induced by augmented input from cardiac "sympathetic afferents"[30].

The sympathetic nervous system plays a pivotal role in the natural history of CHF. When the heart begins to fail a series of neural and hormonal survival adaptations are activated to preserve perfusion pressure and conserve sodium and water. These systems include arterial and cardiopulmonary baroreflexes, natriuretic peptides, nitric oxide, the peripheral chemoreflex, angiotensin II (A-II), endothelin-1 and arginine-vasopressin (AVP)[99] (*Figure 1*). There is early activation of cardiac adrenergic drive, which is, with worsening heart failure, followed by an increasing magnitude of generalized sympathetic activation[84]. Eventually, the adverse consequences of this neurohumoral activation will dominate over the short-term compensatory effects (compensation of a diminished heart function by increase of cardiac rate and contractility, vascular tone, venous return and circulatory filling). They are mediated through down-regulation of beta-receptor function and harmful biological effects on the cardiomyocyte and structural end-organ damage such as cardiac enlargement, hypertrophy and fibrosis begin to develop, secondary to permanently elevated levels of catecholamines, renin, angiotensin and aldosteron[42]. Also, neurohumoral activation is a possible trigger for the heart failure related inflammatory response and its effect on cytokines[17,46].

Besides the negative effects of persistent neurohumoral activation on the heart, peripheral musculature undergoes detrimental structural and functional changes as well[35,60], and the rise in neurohomones is paralleled by an increase in the degree of exercise intolerance[44].

Moreover, there is a more prominent role of the ergoreflex in CHF patients compared to healthy subjects; indirectly, by increased stimulation of the ergoreceptors by lactate accumulation in peripheral muscle, or directly, by increased reflex gain[74].

Pharmacological approach

Attempts have been made to assist or repair the heart by mechanical[23] and electrical devices or surgical intervention[90]. A major component of CHF pharmacological therapy is, however, the suppression of the detrimental influences of neurohumoral activation. Although diuretics, digoxin, adrenergic receptor agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosteron receptor antagonists have greatly reduced mortality[73,91], even with optimal treatment mortality rates remain high. Surveys show that 45-65% of CHF patients die within 5 years[10,82]. This underscores the importance of the ongoing quest to improve current therapy and to develop new therapeutic modalities.

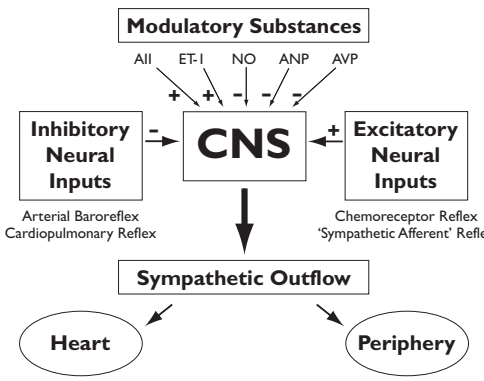

Figure 1. *Neurohumoral excitation depicted as a process consisting of primary sympathetic excitation with neural and humoral feedback at the level of the brainstem. In heart failure, hormonal compounds like angiotensin-II, endothelin-I, nitric oxide, atrial natriuretic peptide and arginine-vasopressin in the circulation are dysregulated, as are the concentrations of these modulatory substances at the level of the brainstem. Obviously, the active function of the blood-brain barrier and local production at the level of the brain result in differences in the peripheral and central concentrations of these compounds. Hence, the levels measured in blood are not fully representative of the concentrations in the brain. However, there is good evidence to support that peripheral and central concentrations parallel each other, thus making the peripherally measured concentrations at least indicative for the degree of feed-back inhibition/excitation at the central level[20,21,41]. Figure reproduced from Zucker et al.[99], with permission.*

Patients with the highest sympathetic activation and patients with the lowest BRS have the poorest survival rate[5,9]. Lowering of plasma catecholamine concentrations and increasing BRS seem logical therapeutic goals, as, in CHF, over time lowered plasma neurohormones and increased BRS are associated with decreased morbidity and mortality[5]. Optimal treatment with adrenergic receptor blockers and angiotensin-converting enzyme inhibitors lowers plasma neurohormones but, unfortunately, the levels remain elevated with respect to normal[52,73]. Beta-blockade may also increase BRS[64,86], however, BRS in CHF patients remains lower than normal.

Exercise training

European and American guidelines[43,90] recommend exercise training in addition to pharmacotherapy. Exercise training lessens dyspnea and fatigue[39,61], improves quality of life, improves New York Heart Association (NYHA) class[6,7,24,68,71,92], decreases morbidity and, likely, also mortality[22,75,81,89]. The beneficial effects of exercise training in CHF have been documented at various functional and structural levels. Although the ELVD-CHF trial[31] reports a slightly increased left ventricular ejection fraction, most studies report hardly any change in this parameter[78]. The generally observed exercise training induced increase in peak oxygen consumption ($\dot{V}O_{2\,peak}$)[81] is presumably mainly attributable to an increase in peak heart rate, an increase in stroke volume during exercise, and peripheral muscular adap-

tations like increased capillary density, blood flow, mitochondrial volume density, fibre size, slow twitch fibres and decreased lactic acidosis and vascular resistance[27,34,38,39,47,76].

In addition to these functional and clinical effects, exercise training in CHF also appears to reduce autonomic derangement and neurohumoral excitation at rest[11]. The mechanisms by which these effects are accomplished are incompletely known; in part, it may be ascribed to neuronal nitric oxide synthase formation in the paraventricular nucleus[98]. By lowering neurohormone plasma concentrations and by reinforcing the arterial baroreflex, exercise training acts in concert with pharmacotherapy in the treatment of CHF patients.

Unfortunately, the effects of exercise training on autonomic derangement and neurohumoral excitation in CHF patients at rest have not been studied or reviewed to the extent of the effects of pharmacological therapy. Only one review[55], merely reiterating the one by Braith and Edwards[11], appeared since 2003. A total of 16 original studies, of which 10 were published after the review by Braith and Edwards[11], were not included in either review article (see *Table 1*). Hence, a recent overview with the merit to update readers and with educational potential to readers not familiar with this topic, is necessary. The recent studies have confirmed and nuanced earlier findings and demonstrated new information in the field, notably the effect of exercise on resting BRS, on resting muscle sympathetic nerve activity (MSNA), and on resting plasma renin, endothelin and brain natriuretic peptide (BNP) concentrations in heart failure. Of these, BRS and BNP have a high prognostic value in CHF and have substantial importance for clinical evaluation and treatment of CHF patients.

REVIEWED STUDIES

We searched MEDLINE and www.scholar.google.com, using the following terms: chronic heart failure, exercise, training, rehabilitation, physical activity, neurohumoral, neurohormones, catecholamines, epinephrine, norepinephrine, angiotensin, aldosteron, brain natriuretic peptide, atrial natriuretic peptide, baroreflex, endothelin, vasopressin, muscle sympathetic nerve activity, heart rate variability. We found 23 original studies addressing the effects of exercise training on autonomic derangement and neurohumoral activation in CHF patients with systolic failure, measured at rest. The main methodological characteristics of all 23 studies are listed in Table 1. Seventeen studies had a control group; 14 of these were randomised controlled trials, while in the other 2 studies no explicit statement about randomisation was made. Six studies had no control group, 3 of these were case series and 3 were crossover trials.

In the 23 reviewed studies, a total of 849 patients (550/299 exercise/control) were included. Nineteen studies enrolled NYHA class II-III patients; Hambrecht et al.[39], Passino et al.[72] and the European heart failure training group[2] included NYHA class I-III patients, while Yeh et al.[97] included NYHA class I-IV patients. In the latter study, training was done by Tai Chi, which is to be classified as exercise with moderate intensity, requiring energy expenditure of approximately 3 to 5 metabolic equivalent (MET) tasks[4]. In the publication by Yeh et al.[97] there is no explicit statement about the training intensity, but it is doubtful whether the Tai Chi was applied at a 3–5 MET intensity level, as NYHA class IV patients are already symptomatic at rest.

Among the reviewed papers, the exercise training programs varied considerably in intensity, training frequency (2 to 7 sessions/week), session duration (15 to 60 minutes), program duration (8 weeks to 6 months) and training modality. The observed effects of exercise on autonomic derangement and neurohumoral excitation, summarized in Tables 2–5, are discussed in the following sections.

RESULTS

Baroreflex and heart rate variability

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 varies from zero to average to maximum when the systolic blood pressure of the given heart beat is very low, equal to, or very high respectively, relative to the average blood pressure level. The afferent baroreceptor burst constitute neural information for the vasomotor centre in the medulla oblongata[70]. 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). Thus, the baroreflex is a negative feedback loop in the neurohumoral excitation process in CHF.

Baroreflex vigor is usually characterized in terms of the extent of bradycardia that occurs when blood pressure increases, and is indicated by the 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 sensitivity in CHF parallels deterioration of clinical and hemodynamic status and is significantly associated with poor survival[65].

Exercise training increases BRS in healthy subjects[13] and in patients with myocardial infarction[54,63]. A significant positive relation was also found between individual exercise-induced BRS improvement and survival[54].

Only 1 study examined the effect of exercise training on resting BRS in patients with CHF (*Table 2*)[77], but unfortunately, this study lacked a control group. The study comprised of a small training group (13 patients), but managed to find a significant training-induced increase in BRS. Controlled studies should verify this interesting finding.

Heart rate variability (HRV) is intimately related to BRS, as it gives a qualitative and quantitative description of the variations in the instantaneous heart rate that are mainly the result of baroreflex-mediated spontaneous blood pressure fluctuations[28,94]. Decreased HRV in CHF patients is likely to be attributed to decreased vagal involvement in cardiovascular control[37]. Reduced HRV (e.g., a reduced standard deviation of the intervals between normal beats, SDNN) has a strong prognostic value and is related to increased mortality in CHF[67].

Because SDNN is one of the most commonly computed HRV parameters, and has the advantage that is not sensitive to algorithmic variants as seen in spectral HRV analysis[1] we have searched the literature for studies towards the influence of exercise training on SDNN in rest in CHF patients. Four such studies[2,3,18,88] were found (*Table 2*). Three studies[2,3,18] reported a significant increase in SDNN at rest after exercise training. Selig et al.[88] did not find any difference after exercise training; however, in this study, the training regimen was restricted to resistance training. In conclusion, aerobic exercise training increases SDNN at rest in CHF patients.

Sympathetic nervous system

Circulating catecholamines originate from the adrenal medulla, in the form of epinephrine and norepinephrine in a ratio of about 80/20%. Catecholamine secretion occurs when the innervating preganglionic sympathetic nerves are activated during times of stress. Circulating catecholamines also originate from spilled-over norepinephrine produced at sympathetic nerve endings throughout the body[50]. In addition to measuring catecholamines in blood, sympathoexcitation can also be assessed by measuring MSNA e.g., in the peroneal nerve; catecholamine levels and MSNA are well correlated during enhanced sympathetic drive[80].

Thirteen studies[2,8,18,33,39,40,48,49,51,72,92,93,97], comprising a total of 481 patients (239/199

Table 1. *Methodological characteristics of the included studies.*

Study	RCT	N (C/T)	M/F		EF% inclusion criteria	EF%		NYHA	Intensity	days/ week	Duration per session	Duration training program	Exercise Modality
			T	C		T	C						
Adamopouos, 1995	No	12	12/0	–	–	19 ± 2	–	II/III	70–80% max HR	5	?	8 weeks	Cycling
Belardinelli, 1995	No	27 (9/18)	16/2	7/2	30 ± 5%	31 ± 5	29 ± 4	II/III	40% $\dot{V}O_{2\,peak}$	3	30–40 min	8 weeks	Cycling
Braith, 1999	Yes	19 (9/10)	?	?	<40%	30 ± 7	30 ± 7	II/III	70%80% $\dot{V}O_{2\,peak}$	?	30–40 min	16 weeks	Walking
Coats, 1992	No	17	17/0	–	–	20± 2	–	II/III	60–80% max HR	5	20 min	8 weeks	Cycling
*Conraads, 2004	No	49 (22/27)	21/6	15/7	<35%	26 ± 1	26 ± 1	II/III	90% of VT/ 50–60% IRM	3	10 min cycling 40 min resistance	4 months	Cycling / Resistance
*European HF training Group, 1998	No	134[1]/43[2]/ 11[3]/57[4]	126/8	–	–	25 ± 9	–	I/II/III	70–80% max HR	4–5	25 min cycling 12 min calisthenetics	6–16 weeks	Cycling/Calisthenics optional
*Gordon, 1997	No	20 (7/13)	13/0	7/0	–	28 ± 3	27 ± 3	II/III	65–75% $\dot{V}O_{2\,peak}$	3	20 min	8 weeks	Knee extensor
Hambrecht, 1995	Yes	22 (10/12)	12/0	10/0	<40%	26 ± 9	27 ± 10	II/III	70% $\dot{V}O_{2\,peak}$	6–7	two 20 min sessions a day	6 months	Cycling/Walking/Calisthenics/ Ball games
*Hambrecht, 2000	Yes	73 (37/36)	37/0	36/0	<40%	27 ± 9	27 ± 9	I/II/III	70% $\dot{V}O_{2\,peak}$	7	20 min	6 months	Cycling/Walking/Calisthenics/ Ball games
*Jónsdóttir, 2005	Yes	43 (22/21)	16/5	18/4	–	42 ± 14	41 ± 14	II/III	50% $\dot{V}O_{2\,peak}$/ 20–40% IRM	2	50 min	5 months	Cycling/Thera-bands/ Resistance
Keteyian, 1999	Yes	51 (25/26)	25/0	26/0	<35%	22 ± 8	22 ± 7	II/III	50–80% HR-reserve	3	33 min	24 weeks	Treadmill/Walking/ Armergometer
Kiilavuori, 1999	Yes	22 (10/12)	12/0	14/1	<40%	24 ± 5	25 ± 7	II/III	50–60% $\dot{V}O_{2\,peak}$	3	30 min	6 months	Cycling
*Kobayashi, 2003	Yes	28 (14/14)	12/2	8/6	<40%	33 ± 2	29 ± 2	II/III	VT	2–3	two 15 min sessions a day	3 months	Cycling
*Larsen, 2004	No	12	12/0	–	–	32 ± 6	–	II/III	80% max HR	3	30 min	12 weeks	Cycling
*De Mello Franco, 2006	Yes	29 (12/17)	13/4	9/3	<40%	29 ± 2	27 ± 3	II/III	10% below VT	3	60 min	4 months supervised, 4 months at home	Cycling/Resistance
*Passino, 2006	Yes	85 (41/44)	39/5	35/6	<45%	35 ± 2	32 ± 2	I/II/III	60% $\dot{V}O_{2\,peak}$	3	30 min	9 months	Cycling
*Pietilä, 2002	No	13	12/1	–	–	36 ± 5	–	II/III	60–85% max HR	6	minimal 30 min	6 months	Light anaerobic muscle training, walking, aerobic, step board, Cycling
*Roveda, 2003	Yes	16 (9/7)	5/2	6/3	<40%	35 ± 3	35 ± 3	II/III	90% of VT	3	60 min	4 months	Cycling/Ground exercise
*Sarullo, 2006	Yes	60 (30/30)	23/7	22/8	<40%	29 ± 5	30 ± 4	II/III	60–70% $\dot{V}O_{2\,peak}$	3	30 min	3 months	Cycling
*Selig, 2004	Yes	39 (20/19)	15/4	18/2	<40%	27 ± 7	28 ± 6	II/III	< within 5 beats/ min of max HR	3	–	3 months	Resistance
*Tyni-Lenne, 1999	Yes	24 (8/8+8)	T:5/3 KT:4/4	4/4	<40%	T:29 ± 13 KT:31 ± 9	30 ± 11	II/III	50–80% HR-reserve	3	30 min	8 weeks	Cycling/Knee extensor
*Tyni-Lenne, 2001	Yes	24 (8/16)	8/8	5/3	<40%	30 ± 9	30 ± 10	II/III	?	3	60 min	8 weeks	Cycling/Knee extensor
*Yeh, 2004	Yes	30 (15/15)	10/5	9/6	<40%	24 ± 7	22 ± 8	I/II/ III/IV	Tai Chi	5	35-60 min	12 weeks	Tai Chi

*C: control group; EF: ejection fraction; F: female; KT: knee extension training group; M: male; max HR: heart rate; RCT: randomised controlled trial; T: exercise training group; VT: ventilatory threshold; 1RM: 1-repetitive maximum; 1: total number of patients; 2: number of patients with noradrenaline measurement; 3: number of patients with adrenaline, plasma renin activity, aldosteron and atrial natriuretic peptide measurement; 4: number of patients with heart rate variability measurement ;?: unknown; *: not reviewed before.*

exercise/control), investigated the effect of exercise on plasma norepinephrine levels or norepinephrine spill-over levels at rest (*Table 3*). Coats et al.[18] found a significant decrease in whole body norepinephrine spill-over in the exercise group, when compared to the control group. Likewise, 4 other studies found significant reduction of norepinephrine plasma resting levels[40,72,92]. Tyni-Lenné et al.[93], in a study with 2 different exercise groups, found a significant decrease in norepinephrine plasma resting levels in the knee extensor training group, but not in the cycling group. None of the 13 studies found a significant increase of norepinephrine in rest. Kobayashi et al.[51] and Yeh et al.[97] found a trend towards an increase in plasma norepinephrine at rest in the training groups[51,97], but, as stated before, the Tai Chi training intensity in the study by Yeh et al. may have been low, while Kobayashi et al. used the shortest session duration of all studies. Possibly, a longer session duration and a higher training intensity are needed to lower norepinephrine plasma concentrations at rest.

Six studies measured the effect of exercise on plasma epinephrine at rest (*Table 3*)[2,8,33,39,40,51]. Three studies[39,40] showed a significant reduction of plasma epinephrine in the exercise group, in 1 controlled study there was a nonsignificant trend of plasma epinephrine reduction in the exercise group[8]. Another controlled study showed no change at all[70]. Gordon et al.[33] found in an uncontrolled study a nonsignificant upward trend in plasma epinephrine at rest.

Two studies[62,83] investigated the effect of exercise on MSNA at rest and found a substantial decrease in resting MSNA after exercise training. Roveda et al.[83] even found that resting MSNA levels in trained heart failure patients were even comparable to MSNA levels in trained healthy controls (*Table 3*).

In conclusion, the controlled studies report a significant decrease in sympathoexcitation at rest, with the exception of the studies by Kobayashi et al.[51], Yeh et al.[97] and Kiilavuori et al.[49]. As the latter 2 studies used very brief training sessions or very low intensity exercise, respectively, we conclude that exercise training with reasonable frequency, duration and intensity decreases sympathoexcitation at rest in CHF patients.

Renin-angiotensin-aldosteron system

The renin-angiotensin-aldosteron system (RAAS) is the primary mechanism for volume control[96]. Sympathetic stimulation increases the formation of renin (mainly produced by the juxtaglomerular kidney cells), that stimulates the formation of angiotensin I from angiotensinogen (produced in the liver). Then, A-II is formed from angiotensin I by angiotensin converting enzyme (produced in the lungs). Finally, A-II enhances the release of aldosteron from the adrenal glands[53]. In addition to acting on circulating volume and vascular resistance, A-II and aldosteron are also involved in hypertrophy and collagen synthesis in the heart[69].

One important effect of A-II with respect to the process of neurohumoral activation is that it facilitates the production of norepinephrine, and, at the level of the central nervous system, has a sympathoexcitatory action[99]. In addition, aldosteron inhibits nitric oxide production[16] and the arterial baroreflex[87]; both would, at the

Table 2. *The effect of exercise training in CHF on baroreflex sensitivity and heart rate variability at rest.*

	BRS			HRV		
Study	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**
Adamopoulos, 1995				–	↑*18%	–
Coats, 1992				–	↑*15%	–
European HF training Group, 1998				–	↑*13%	–
Pietilä, 2002	–	↑*74%	–			
Selig, 2004				5%↓	5%↓	↔

BRS: baroreflex sensitivity; C: relative change (baseline vs placebo) in the control group; HRV: heart rate variability; T: relative change (baseline vs intervention) in the training group; T vs C: change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; ↓: decrease; ↑: increase; ↔: no changes were found; ?: unknown significance level; *: significant change, $P<0,05$.

Table 3. *The effect of exercise training in CHF on norepinephrine, epinephrine and muscle sympathetic nerve activity at rest.*

	NE			E			MSNA		
Study	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**
Belardinelli, 1995	–	↓ 16%	↔	–	↓21%	↔			
Coats, 1992	–	↓* 16%	–						
European HF training Group 1998	–	↓* 23%	–	–	↓* 53%	–			
Gordon, 1997	–	↓ 10%	–	–	↑25%	–			
Hambrecht, 1995	↓52*%	↓* 52%	↔	↓*	↓* 50%	↔			
Hambrecht, 2000	↓ 31%	↓ 31%	↔	↓*	↓?	↑?			
Keteyian, 1999	↓18%	↓ 17%	↑1%						
Kiilavuori, 1999	–	↓ 19%	↓?						
Kobayashi, 2003	↑ 16%	↑37%	↑ 21%	↔	↔	↔			
de Mello Franco, 2006							45%S↓* 33%H↓	29%S↓* 17%H↓	16%↑
Passino, 2006	↓44%	↓*26%	↑18%						
Roveda, 2003							↓* 46%	↓* 48%	↓ 2%
Tyni-Lenne, 1999	–	↓knee* ↔Cycling	–						
Tyni-Lenne, 2001	↓*32%	↓* 26%	↑ 6%						
Yeh, 2004	↑29%	↑ 46%	↑17%						

C: relative change (baseline vs placebo) in the control group; E: epinephrine; MSNA: muscle sympathetic nerve activity; NE: norepinephrine; T: relative change (baseline vs intervention) in the training group; T vs C: change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; ↓: decrease; ↑: increase; ↔: no changes were found; ?: unknown significance level; *: significant change, $P<0,05$.

central level, result in additional sympathoexcitation[99]. Hence, the RAAS acts as a positive feedback loop in the process of neurohumoral activation.

Three studies[2,12,72] examined the effect of exercise on resting RAAS parameters (*Table 4*). Braith et al.[12] found a significant decrease in A-II and aldosteron plasma levels at rest in the exercise group, reaching values comparable to those of sedentary healthy subjects. Although this study had a randomized controlled setup, no explicit information about the statistical comparison between the RAAS parameter changes in the exercise training group as compared to the changes in the control group was presented. Passino et al.[72] and the European Heart Failure Training Group[2] didn't find any significant differences in plasma renin activity or aldosteron plasma levels.

In conclusion, the available data are controversial and more research is necessary to verify the effect of exercise on resting RAAS activity in CHF

Arginine-vasopressin

Arterial underfilling, low cardiac output, rising osmolarity and increased A-II levels activate the hypothalamo-pituitary-adrenal axis that interacts with the sympathetic nervous system-RAAS axis to maintain cardiovascular and metabolic homeostasis[57]. As a consequence, AVP is released from the posterior pituitary. AVP increases water reabsorption by the kidneys, and, in high concentrations, constricts arterial blood vessels. CHF patients may have two- to threefold elevated AVP plasma levels[32], causing the already increased systemic vascular resistance to rise even further. The feedback action of AVP in neurohumoral activation process is not completely elucidated. Predominantly negative feedback effects by AVP have been described at the central level. Stimulation of V1b receptors in the medulla causes catecholamine secretion (positive feedback)[25], while AVP produces adrenocorticotropic hormone and beta-endorphins at the pituitary level[15,57] and AVP increases BRS[66]. Beta-endorphins and the arterial baroreflex suppress sympathetic activity (negative feedback)[14].

The study by Braith et al.[12] (*Table 4*) is the only study that addresses the effect of exercise on resting AVP levels in CHF. The paper reports a significant AVP reduction in the exercise group, whereas levels in the control group remained unchanged.

Endothelin

Hypoxia, shear stress, catecholamines and A-II stimulate endothelial cells to release endothelin[58]. Endothelin levels are considerably increased in patients with NYHA class III/IV[95]. Endothelin causes arterial vasoconstriction, myocardial and vascular cell hypertrophy and aldosteron release; endothelin diminishes sodium excretion and leads to sympathoexcitation. As such, endothelin closes a positive feedback loop in the process of neurohumoral excitation.

Kobayashi et al.[51] examined the effect of exercise on endothelin (*Table 5*). Resting endothelin plasma concentrations showed a nonsignificant decreasing trend (-4%) in the training group, and a nonsignificant increasing trend (16%) in the control group, with no significant difference between the 2 groups. The number of patients enrolled in this study was small (N=28), and new studies should verify the effect of exercise training on resting endothelin concentrations in patients with CHF.

Natriuretic peptides

When the compensatory actions of the sympathetic nervous system-RAAS and hypothalamo-pituitary-adrenal axes lead to a state of cardiac overload, the humoral emergency system of the natriuretic peptides is activated. Release of atrial natriuretic peptide (ANP) and BNP occurs under influence of increased preload and afterload, contractility, heart rate, catecholaminergic stimulation, A-II and endothelin[79,85]. Natriuretic peptides have diuretic and vasodilatory activity and inhibit aldosteron secretion. Also, ANP attenuates

Table 4. *The effect of exercise training in CHF on plasma renin activity, angiotensin II, aldosterone, vasopressin and endothelin at rest.*

	Plasma renin activity			Angiotensin II			Aldosterone			Vasopressin		
Study	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**
Braith, 1999				↓?30%	↓*26%	↑4%	↓?35%	↓* 32%	↑3%	↓?34%	↓* 30%	↑4%
European HF training Group, 1998	-	↓12%	-				-	↓1%	-			
Passino, 2006	↑1%	↓3%	↓4%				↓17%	↓6%	↑11%			

C: relative change (baseline vs placebo) in the control group; T: relative change (baseline vs intervention) in the training group; T vs C: change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; ↓: decrease; ↑: increase; ?: unknown significance level; *: significant change: $P<0,05$.

Table 5. *The effect of exercise training in CHF on endothelin, brain natriuretic peptide and atrial natriuretic peptide at rest.*

	Endothelin			BNP/NT-proBNP			ANP/NT-proANP		
Study	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**	**T vs C**	**T**	**C**
Braith, 1999							↓?33%[3]	↓* 27%[3]	↑6%[3]
Conraads, 2004				↓*21%[2]	↓* 23%[2]	↓2%[2]			
European HF training Group, 1998							-	↓7%[3]	-
Gordon, 1997							↓27%[3]	↓* 27%[3]	↔0%[3]
Jónsdóttir, 2005				↓3%[1]	↓1%[1]	↑2%[1]	↑3%[3]	↑5%[3]	↑2%[3]
Kiilavuori, 1999								↔[3]	
Kobayashi, 2003	↓20%	↓ 4%	↑ 16%	↓ 5%[1]	↓ 5%[1]	↔0%[1]			
Larsen, 2004							-	↑10%[4]	-
Passino, 2006				↓*41%[1] ↓*38%[2]	↓*34%[1] ↓*32%[2]	↑7%[1] ↑6%[2]			
Sarullo, 2006				↓*49%[2]	↓*58%[2]	↓9%[2]			
Yeh, 2004				↓*47%[1]	↓15%[1]	↑ 32%[1]			

ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; C: relative change (baseline vs placebo) in the control group; T: relative change (baseline vs intervention) in the training group; T vs C: change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; ↓: decrease; ↑: increase; ↔: no changes were found; ?: unknown significance level; *: significant change, $P<0,05$; [1]: BNP; [2]: NT-proBNP; [3]: ANP; [4]: NT-proANP.

norepinephrine release from sympathetic nerve terminals as well as (by central action) sympathetic outflow. As such, the natriuretic peptides form a negative feedback loop in the process of neurohumoral activation in CHF. As an emergency system, elevation of ANP (atrial volume overload), and certainly elevation of BNP (ventricular pressure overload) have a strong predictive value: a 100 pg/ml increase of BNP plasma levels results in a 35% higher risk of death[26]. Some investigators prefer the measurement of NT-pro BNP/NT-pro ANP over the BNP or ANP plasma levels because of their larger half-time life.

The effect of exercise on BNP/NT-pro BNP resting levels in plasma was investigated in 6 of all reviewed studies (*Table 5*)[19,45,51,59,72,97]. Yeh et al.[97] found a decreasing trend in plasma BNP resting levels in the training group and an increasing trend in the control group, resulting in a significant difference between the 2 groups. Conraads et al.[19], Sarullo et al.[59] and Passino et al.[72] found a significant decrease of NT-pro BNP resting levels in the training group and the difference between the training group and the control group was also significant, where Passino et al.[72] found the same results also for BNP resting levels. Finally, Kobayashi et al.[51] and Jónsdóttir et al.[45] found no significant effect of exercise training on resting BNP levels. These differences might be explained by the larger half-time life of NT-pro BNP.

In 6 studies, the effect of exercise on resting ANP/NT-proANP levels in plasma was investigated (*Table 5*)[2,12,33,45,49,56]. Two studies[12,33] found in the training group a significant decrease in resting ANP levels to within the reference interval (ANP <32 pmol/L). Four studies[2,45,49,55] found no significant differences in resting ANP or NT-pro ANP levels, in two of them[45,49] the training intensity applied in these studies was lower than that employed in the studies of Braith et al.[12] and Gordon et al.[33], respectively 50-60% of $\dot{V}O_{2\,peak}$ against 65-85% of $\dot{V}O_{2\,peak}$. A higher training intensity may be needed for lowering resting ANP levels.

In conclusion, training had no adverse effects on resting levels of natriuretic peptides. The available data on ANP/NT-pro ANP are controversial and more research is necessary to verify the effect of exercise on resting RAAS activity in CHF. Also exercise training decreased resting NT-pro BNP levels in patients with CHF, although BNP resting levels did not always decrease after exercise training.

CONCLUSION

In conclusion, exercise training has beneficial direct and reflex sympathoinhibitory effects in CHF. Also, evidence exists for the normalization of other components of neurohumoral excitation as a consequence of exercise training. Thus, exercise training directly competes with the pathophysiological afferent stimuli from the failing heart that tend to permanently increase sympathetic outflow, leading to autonomic derangement and neurohumoral activation. Therefore exercise training is an important complementary therapy for CHF patients on stable medication.

The mechanism responsible for the normalisation of the neurohumoral activation and autonomic derangement by exercise training is not yet clarified. Knowledge of the key elements of an exercise program that are responsible to achieve a training effect would allow designing training programs specific for CHF patients, with maximal efficacy at minimal work load, to meet their limited exercise tolerance. Also, follow-up studies are needed to determine whether normalization of exercise induced neurohumoral excitation and autonomic derangement in CHF patients is associated with improved prognosis.

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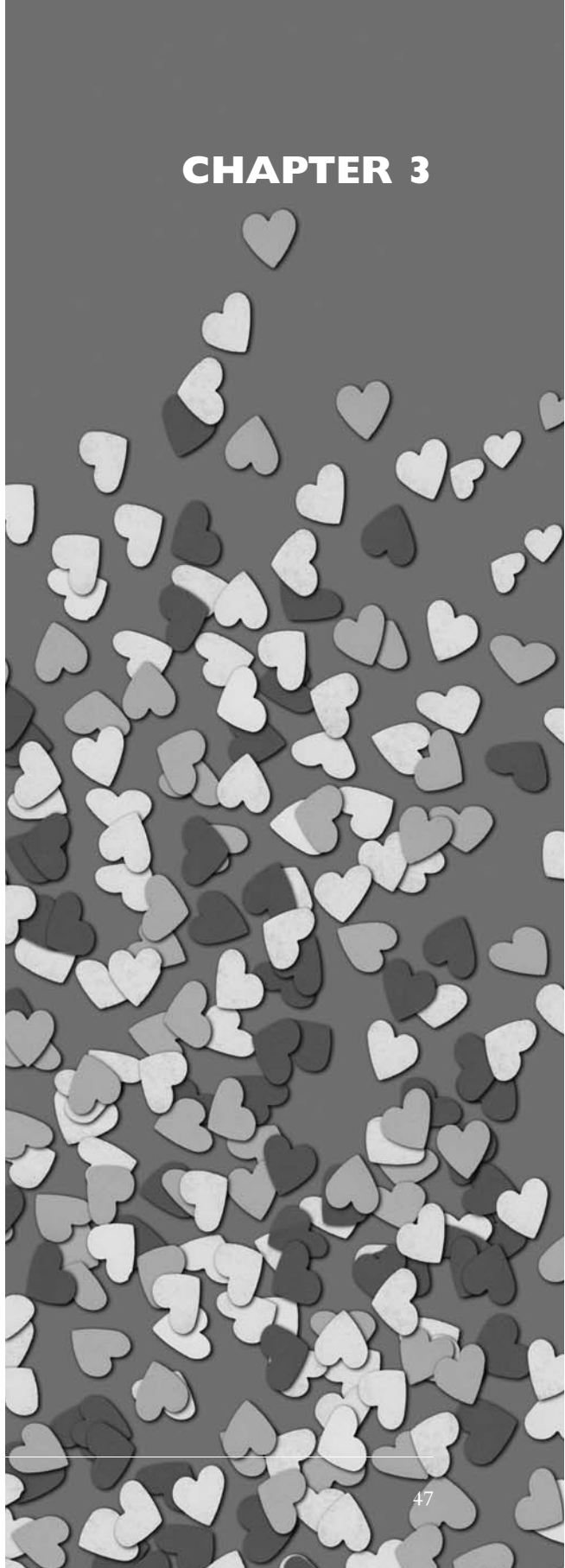
CHAPTER 3



BAROREFLEX SENSITIVITY, BLOOD PRESSURE BUFFERING AND RESONANCE: WHAT ARE THE LINKS? COMPUTER SIMULATION OF HEALTHY SUBJECTS AND HEART FAILURE PATIENTS

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ABSTRACT

Objectives. The arterial baroreflex buffers slow (< 0.05 Hz) blood pressure (BP) fluctuations, mainly by controlling peripheral resistance. Baroreflex sensitivity (BRS), an important characteristic of baroreflex control, is often noninvasively assessed by relating heart rate (HR) fluctuations to BP fluctuations; more specifically, spectral BRS assessment techniques focus on the BP to HR transfer function around 0.1 Hz. Scepsis about the relevance of BRS to characterize baroreflex-mediated BP buffering is based on two considerations: 1) baroreflex modulated peripheral vasomotor function is not necessarily related to baroreflex-HR transfer, and 2) though BP fluctuations around 0.1 Hz (Mayer waves) might be related to baroreflex blood pressure buffering, they are merely a not-intended side-effect of a closed loop control system.

Methods. To further investigate the relationship between BRS and baroreflex-mediated BP buffering, we set up a computer model of baroreflex BP control to simulate normal subjects and heart failure patients. Output variables for various randomly chosen combinations of feedback gains in the baroreflex arms were BP resonance, BP buffering capacity and BRS.

Results. BP buffering and BP resonance are related expressions of baroreflex BP control and depend strongly on the gain to the peripheral resistance. BRS is almost uniquely determined by the vagal baroreflex gain to the sinus node.

Conclusions. BP buffering and BRS are unrelated unless coupled gains in all baroreflex limbs are assumed. Hence, the clinical benefit of a high BRS is most likely to be attributed to vagal effects on the heart instead of to effective blood pressure buffering.

INTRODUCTION

In daily life, multiple processes perturb blood pressure. The duration of these challenges varies widely. For example, respiration makes blood pressure fluctuate with every breath[13] while physical or mental stress elevate blood pressure for minutes or even longer. The arterial baroreflex is a negative feedback mechanism that effectively buffers such incidental blood pressure fluctuations[11,20,21,23]. In negative feedback systems, feedback delay often causes resonance in a given frequency band; this is the price to be paid for effective buffering at other frequencies. Resonance in blood pressure[5,8,12,31,49] manifests in the form of the well known Mayer[22,33] waves (beat-to-beat blood pressure oscillations with a frequency around 0.1 Hz / periodicity around 10 s). Effective baroreflex blood pressure buffering occurs below the Mayer frequency[10,16].

Besides a sympathetic limb that modulates peripheral resistance, the baroreflex has also sympathetic and parasympathetic (vagal) limbs that influence cardiac contractility, venous return and cardiac rhythm. Usually, baroreflex functioning is characterized by baroreflex sensitivity (BRS). This index of baroreflex vigor is defined as the reflex-induced change in interbeat interval in ms per mmHg blood pressure change[14,34,36,44]. The prognostic value of BRS, and the favorable consequences of successful interventions with BRS, has amply been demonstrated[27,28].

Little is known, however, about the representativeness of this index for the efficacy of blood pressure buffering. There are two reasons to be skeptical in this respect:

1) By definition — interbeat interval change per unit blood pressure change — BRS is bound to characterize baroreflex mediated effects on the heart, while the baroreflex buffers blood pressure mainly by controlling peripheral resistance[2,30]
2) Oftentimes being assessed in the Mayer frequency range of spontaneous heart rate and blood pressure fluctuations[15,39], BRS might represent resonance- rather than buffering baroreflex characteristics.

We addressed these skepticisms by simulations with a hybrid mathematical model of baroreflex blood pressure and heart rate control, composed of hemodynamic elements that are evaluated on a beat to beat basis, linked to a time-continuous modeled neural control part. By changing some parameter settings the model mimics physiological as well as pathological hemodynamic and autonomic conditions.

By simulating with various gain combination values, we quantified the role of the sympathetic and parasympathetic gains in the three baroreflex limbs for blood pressure variability (BPV) and heart rate variability (HRV) under physiologic and pathologic conditions. From the obtained systolic blood pressure and interbeat interval values, relations between BRS and blood pressure buffering, and between blood pressure buffering and resonance were examined.

METHODS

The simulation model we used for this study represents short-term human blood pressure control without breathing modulation. It is tuned for supine posture. This model — programmed in Matlab Simulink (*The MathWorks, Inc., Natick*, MA) — is, apart from some modifications, similar to the model as earlier designed and validated by TenVoorde and Kingma[46].

Model description

A gross overview of the autonomically controlled model is given in *Figure 1* (see *Table 1* and *Table 2* for abbreviations and model parameters). The model represents the systemic circulation and consists of three sections: a hemodynamic section, a baroreceptor section and an autonomic control section. The model generates output in the form of time dependent systolic blood pressure values (SBP, mmHg) and interbeat interval values (IBI, ms) by using a sinusoidal pressure probe (frequency adjustable, amplitude fixed at 1 mmHg) as an input signal. This apparently small perturbation at the input of the baroreflex produces reduced SBP fluctuations (amplitude <1 mmHg,

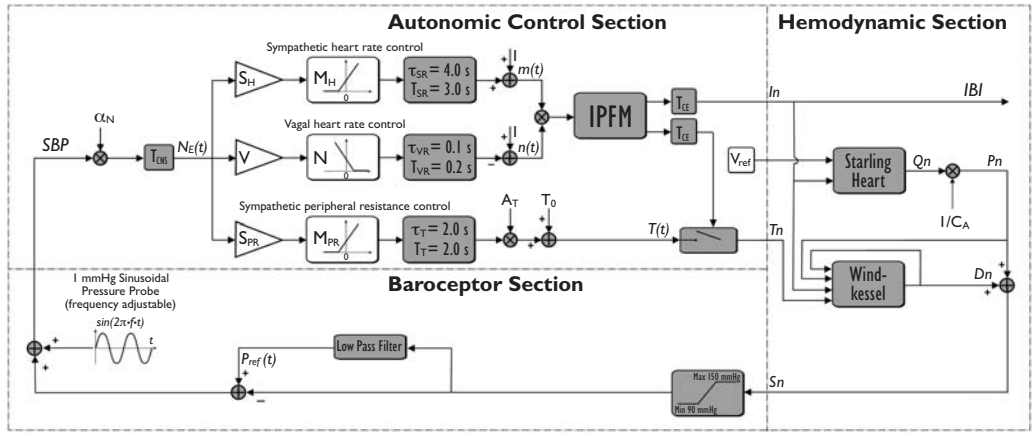

Figure 1. *Model of baroreflex arterial blood pressure control. The model variables and model parameters are described in Table 1 and Table 2. Model sections and parameters are discussed in the Methods section. Note that variables (i.e., continuous signals and sample and hold signals) are denoted italic. Adjustable parameters (denoted bold) are placed in white boxes, fixed model divisions are placed in grey boxes.*

buffering) but also Mayer waves (amplitude >1 mmHg, resonance), depending on the frequency of the pressure probe.

Hemodynamic section

In the hemodynamic section, all signals are sample-and-hold signals: the beat-to-beat varying cardiovascular signals are modeled in elementary difference equations. All values are adapted when a new heartbeat emerges. Stroke volume Q_n is produced by the one-chamber Starling heart. It depends on interbeat interval I_n, venous return volume V_n and a contractility volume term C_n:
$Q_n = \delta_n \cdot V_n + C_n$,
where δ_n is a left ventricle filling factor:
$\delta_n = 0.5 + 0.5\, I_n / 1000$.
As this model will only be used to simulate different autonomic control states, rather than different hemodynamic states (like standing posture), changes in cardiac contractility and venous return appear to generate only very small fluctuations in stroke volume (<5%). Therefore, we simplified above relation into:
$Q_n = \delta_n \cdot V_{ref}$,
where Starling heart filling parameter V_{ref} indicates the stroke volume when $\delta_n = 1$.
Stroke volume, Q_n, assuming a constant arterial compliance C_A, determines pulse pressure P_n by: $P_n = Q_n / C_A$.
A systemic Windkessel simulates diastolic blood pressure D_n:

$$D_n = \left(D_{n-1} + \frac{1}{2}P_{n-1}\right)e^{-\frac{I_n}{T_n}}.$$

The Windkessel time constants T_n is controlled by the baroreflex (see autonomic control section), and is directly associated with total peripheral resistance. Although it is usual to compute diastolic pressure as the exponential decay of systolic pressure, we used this slightly modified formula to obtain more accurate systolic blood pressure values. Finally, systolic pressure S_n is computed by adding P_n and D_n.

Table 1. *Model parameters and values under physiological (phys.) and pathological (path.) conditions.*

Symbol	Description	Value
A_T	Sympathetic peripheral resistance control sensitivity coefficient	11500 ms/nu
α_N	Baroreceptor sensitivity coefficient	0.004 nu/mmHg
f	Pressure probe frequency	0.0033 – 0.3 Hz
M_H	Sympathetic tone to the heart	1.2 (phys.) / 1.5 (path.)
M_{PR}	Sympathetic tone to the peripheral vasculature	1.2 (phys.) / 1.25 (path.)
N	Vagal tone to the heart	0.5 (phys.) / 0.6 (path.)
R_0	Intrinsic heart rate	100 beats/min [25]
S_H	Sympathetic baroreflex gain to the heart multiplier	0.0 – 3.0
S_{PR}	Sympathetic baroreflex gain to the peripheral resistance multiplier	0.0 – 3.0
T_o	Sympathetic peripheral resistance control intrinsic value	1800 ms
T_{SR}	Sympathetic heart rate control time delay	3000 ms [48]
t_{SR}	Sympathetic heart rate control time constant	4000 ms [48]
T_T	Sympathetic peripheral resistance control time delay	2000 ms
τ_T	Sympathetic peripheral resistance control time constant	2000 ms
T_{VR}	Vagal heart rate control time delay	200 ms [35]
τ_{VR}	Vagal heart rate control time constant	100 ms [4,26]
T_{CE}	Delay of cardiac event from SA-trigger to pressure rise	250 ms
T_{CNS}	Delay in central nervous system processing	100 ms [24]
V	Vagal baroreflex gain multiplier	0.0 – 3.0
V_{ref}	Stroke volume at 1000 ms filling time	80 ml (phys.) / 60 ml (path.)

Baroreceptor section

The baroreceptors are modeled linearly within a range of threshold of 90 mmHg and saturation level of 150 mmHg. At the baroreceptors, the systolic blood pressure S_n is compared with a low-pass filtered systolic blood pressure reference value. This value functions as a dynamic blood pressure set point, mimicking the physiologic process of baroreceptor resetting[47,50,51]. The pressure variability source is added at the input of the baroreflex, rendering a sample and hold systolic blood pressure variability signal SBP, the first model output signal.

Autonomic control section

In the time-continuous autonomic control section, SBP is converted into an afferent neural signal N_E by factorizing this signal by the baroreceptor sensitivity coefficient α_N. This signal concerns as input for three effectors:
- vagal heart rate control (output: vagal signal *n*);
- sympathetic heart rate control (output: sympathetic signal *m*);
- sympathetic peripheral resistance control (output Windkessel time constant *T*);

The vagal signal *n* represents vagal heart rate deceleration ($0<n<1$), while the sympathetic signal *m* represents sympathetic heart rate acceleration ($m>1$).

The three effectors are modeled in frequency-dependent functional blocks, with specific sensitivity coefficients, time constants, time delays and by autonomic tones (N, M_H and M_{PR}; see *Table 1* for actual values). In addition to these model parameters, extra baroreflex gain multipliers (S_H, V and S) were added to strengthen or weaken the role of each baroreflex effector.

The neural time-continuous part and the hemodynamic beat-to-beat part are interconnected by an Integral Pulse Frequency Modulator (IPFM), which simulates cardiac pacemaker function[18]. Rosenblueth and Simeone[40] have demonstrated that combined sympathetic and vagal influences on the sinus node contribute to the actual heart rate *R* according to the following relationship: $R = R_o \cdot m \cdot n$, where R_o is the intrinsic heart rate. Integration of incoming neural activity results in the generation of the heart interval length I_n[18]. This interbeat interval IBI is the second model output signal.

Adjustable model parameters

Thus, the model is controlled by seven parameters: one (V_{ref}) for stroke volume, three (M_H, N and M_{PR}) for autonomic outflow, and three (S_H, V and S_{PR}) multipliers for the gains in the three baroreflex limbs.

The first four parameters for stroke volume and autonomic outflow were set as two fixed

Table 2. *Model variables: sample and hold (n) or time dependent (t). bpm: beats per minute*

Symbol	Description	Unit
Dn	Diastolic blood pressure	mmHg
δn	Left ventricle filling factor	-
I_n, IBI	Interbeat interval	ms
m(t)	Sympathetic heart rate acceleration signal	-
n(t)	Vagal heart rate deceleration signal	-
$N_E(t)$	Neural error driving signal	nu
P_n	Pulse pressure	mmHg
$P_{ref}(t)$	Reference systolic blood pressure	mmHg
Q_n	Stroke volume	ml
R(t)	Heart rate	bpm
S_n, SBP	Systolic blood pressure	mmHg
t	Simulation time	s
T_n, T(t)	Windkessel time constant	ms
Vn	Venous return (expressed in blood volume units)	ml

combinations (*Table 1*) to represent either normal physiological, or abnormal pathological resting conditions. With an increased sympathetic tone to the heart and to the peripheral resistance, and decreased parasympathetic tone and reference stroke volume, the pathological parameter settings represent a serious pathologic condition resembling congestive heart failure. Compared to the physiological conditions, the resting heart rate is higher (90 bpm instead of 60 bpm), and the average systolic blood pressure is slightly lower (114 mmHg instead of 120 mmHg).

The last three parameters serve as potentiometers (multipliers) on the vagal and sympathetic baroreflex gains to the heart and to the peripheral resistance;
$V = S_H = S_{PR} = 1$ is the reference value that is to represent a normally working baroreflex.

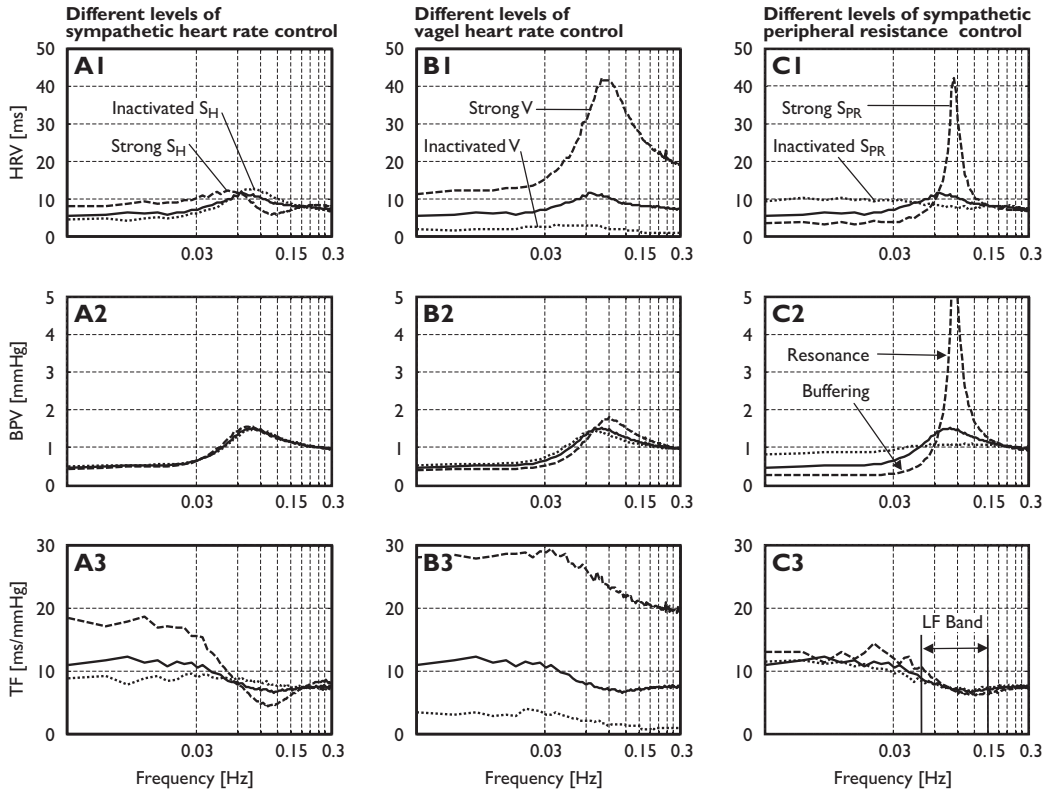

Figure 2. *Examples of simulated heart rate variability (HRV; A1, B1, C1), blood pressure variability (BPV; A2, B2, C2) and transfer function (TF; A3, B3, C3) frequency characteristics. Note that frequency axes are log scaled. For these simulations, the model parameters for stroke volume and autonomic outflow, –V_{ref}, M_H, M_{PR} and N–, were kept fixed at physiological values (see Table 1). The baroreflex gain multipliers S_H, V and S_{PR} were varied around $S_H/V/S_{PR}$ = 1/1/1 (solid line in all panels) in the following way:*
Panels A: dotted line: $S_H/V/S_{PR}$ = 0/1/1 (inactivated S_H), dashed line: $S_H/V/S_{PR}$ = 3/1/1 (strong SH);
Panels B: dotted line: $S_H/V/S_{PR}$ = 1/0/1 (inactivated V), dashed line: $S_H/V/S_{PR}$ = 1/3/1 (strong V);
Panels C: dotted line: $S_H/V/S_{PR}$ = 1/1/0 (inactivated SPR), dashed line: $S_H/V/S_{PR}$ = 1/1/3 (strong SPR).
BPV and HRV amplitudes have to be related to the driving force of the sinusoidal pressure probe (1 mmHg).
BPV = blood pressure variability (amplitude of SBP fluctuations); HRV = heart rate variability (amplitude of IBI fluctuations); TF = modulus of the SBP-to-IBI transfer function.

When one of these parameter values equals 0, the corresponding limb of the baroreflex does not react to changes of SBP with respect to the reference value and the corresponding effector output becomes the (fixed) tone. A value of 0.5 corresponds to weak involvement. The maximum value of these parameters is 3; this value corresponds to a strong involvement of a given baroreflex limb, e.g., as found in highly trained subjects.

Simulations and frequency characteristics

For a given combination of the seven model parameter values, 100 simulation runs were done. A single simulation run served to determine one SBP variability (BPV) frequency component, one IBI variability (HRV) frequency component and the modulus of the SBP-TO-IBI transfer function (TF, necessary to compute BRS) frequency component, at a given frequency of the sinusoid pressure probe. A single simulation run was executed as follows. First, the model was run till steady state conditions were met. Then, cubic splines were fitted through the resulting output signals to obtain the amplitudes of the SBP- and IBI fluctuations, caused by the pressure probe. Finally, the corresponding TF frequency component was computed by dividing HRV (the amplitude of the IBI fluctuations) by BPV (the amplitude of the SBP fluctuations). The 100 simulation runs were done to construct the complete frequency characteristics of BPV, HRV and TF by computing all frequency components between 0.003 Hz and 0.300 Hz (step 0.003 Hz).

A total of 162 frequency characteristics of HRV, BPV and TF were made for both the physiological as well as for the pathophysiological conditions. These 162 frequency characteristics were made to represent 162 different combinations of baroreflex gain multiplier settings. One-hundred fifty gain multiplier combinations were randomly chosen to simulate uncoupled baroreflex gains (values between 0 and 3 from uniform distributions for V, S_H and S_{PR}). In addition, 12 other $V/S_H/S_{PR}$ combinations were made to simulate coupled baroreflex gains (0.5/0.5/0.5, 1/1/1, 1.5/1.5/1.5, 2/2/2, 2.5/2.5/2.5, 3/3/3). Besides these multiplier combinations, an extra set of simulation results (obtained with $V/S_H/S_{PR}$ combinations 0/1/1, 3/1/1, 1/0/1, 1/3/1, 1/1/0, 1/1/3) was made for the generation of *Figure 2*.

Main derived simulation variables: BRS, SBP buffering capacity, SBP resonance

After having computed a full BPV, HRV and TF characteristic, we determined the following variables. BRS was computed as the averaged magnitude of TF in the low-frequency (LF, 0.05-0.15 Hz)[15,37,39]. This band incorporates the Mayer frequencies. SBP *buffering capacity* was expressed as the amplitude of the original perturbation (the 1 mmHg sinusoidal pressure probe) divided by the BPV amplitude at the lowest simulated frequency component (0.0033 Hz, which is still well above the baroreceptor resetting frequency[47]). E.g., when the BPV at the lowest frequency component had an amplitude of 0.25 mmHg, the buffering capacity was 4. Maximal SBP *resonance* (in the LF band) was expressed as the maximal BPV divided by the amplitude of the original perturbation. To determine the relative importance of V, S_H and S_{PR} for BRS and blood pressure buffering/resonance, multiple linear regressions were done. For these regressions, only the simulations made with random generated baroreflex gain multipliers were used.

RESULTS

The simulation results obtained under physiological and pathological conditions (see Table 1) differ quantitatively (more outspoken characteristics under physiological conditions) rather than qualitatively: all frequency characteristics are smooth, and buffering occurs at the lowest frequencies while resonance occurs at the Mayer frequency around 0.1 Hz. *Figure 2* displays examples of some HRV-, BPV- and TF

frequency characteristics obtained under physiological conditions. This Figure consists of three sets of HRV, BPV and TF frequency characteristics, in each of which one of the three effectors was weakened or strengthened, i.e., baroreflex gain multipliers, V, S_H, or S_{PR} was increased to 3 (strong) or reduced to 0 (inactivated) with respect to the default value of 1 (normal), while the other two baroreflex gain multipliers were kept at their default values of 1 (normal).

Panel A3 shows an unexpected influence of sympathetic heart rate control on IBI: the transfer function in the LF band (i.e. BRS) even decreases when control is strengthened (strong S_H). Obviously, blood pressure buffering and resonance are completely insensitive for changes in the sympathetic gain to the heart (panel A2).

Panels B1-B3 show how the HRV, BPV and TF frequency characteristics react when the

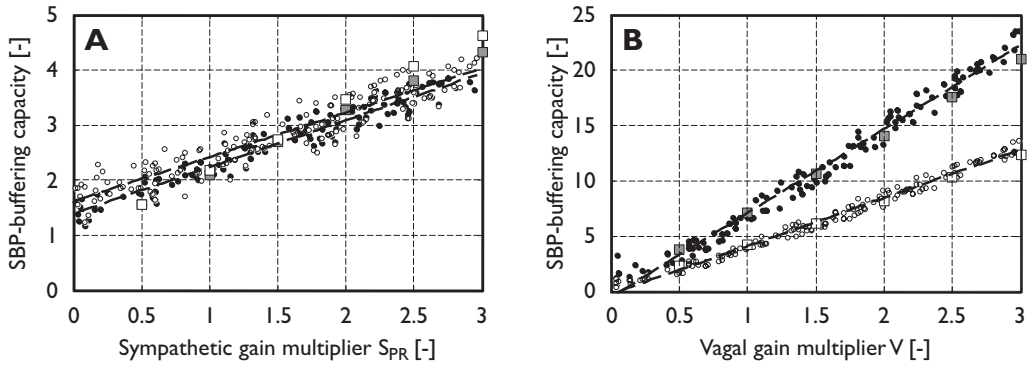

Figure 3. *Main graphical representations of the simulation results. Panel A: systolic blood pressure (SBP) buffering capacity increases with increasing sympathetic baroreflex gain to the peripheral resistance. Panel B: baroreflex sensitivity (BRS) increases with increasing vagal baroreflex gain to the heart. Panel C: SBP resonance increases with increasing SBP buffering capacity. Panel D: SBP buffering capacity is only weakly related to baroreflex sensitivity. Filled circles and squares: physiological conditions; open circles and squares: pathological conditions. Circles (small): simulations with uncoupled (random generated) baroreflex gain multiplier combinations; squares (larger): simulations with coupled baroreflex gain multiplier combinations: $S_H/V/S_{PR}$ = 0.5/0.5/0.5, 1/1/1, 1.5/1.5/1.5, 2/2/2, 2.5/2.5/2.5, 3/3/3. Dashed lines: linear regressions in the random data (hence, scouting simulations with coupled baroflex gain multiplier combinations excluded). See text for further explanation.*

vagal heart rate control is weakened or strengthened (multiplier V assumes the value 0 or 3 respectively, multipliers S_H and S_{PR} are kept at a value of 1). Here, the impression arises that multiplier V strongly influences HRV and the BRS, while it does not affect the resonance and buffering behavior (relatively little differences in resonance and buffering are seen in panel B2).

Panels C1-C2 show the striking effect of a strengthened sympathetic peripheral resistance control (multiplier S_{PR} assumes the value of 3, multipliers V and S_H are kept at a value of 1) on the HRV and BPV frequency characteristics. Panel C2 shows that the original sinusoidal disturbance of SBP by the 1 mmHg pressure probe (see *Figure 1*) is strongly weakened (buffered) for the lowest frequencies, is amplified (resonance) over nearly the whole LF band, and returns to about 1 mmHg for higher frequencies. Larger part of this effect — especially the resonance phenomenon — disappears under normal control (multiplier S_{PR} assumes the value of 1). The frequency characteristic is almost flat when control is absent (multiplier S_{PR} assumes the value of 0). The shapes of the HRV frequency characteristics in panel C1 grossly follow the BPV characteristics. As expected, the TF frequency characteristics (panel C3) are very much similar for all three S_{PR} values 0, 1 and 3. In summary, from frequency characteristics C1-C3 the impression arises that sympathetic peripheral resistance control strongly influences resonance and buffering while it does not affect the TF or BRS.

Figure 3 depicts the strongest relations between vagal and sympathetic baroreflex gains, SBP buffering capacity, SBP resonance and BRS, based on the results of multiple linear regression analysis. It pointed out that in a physiological setting 83% of the variance in SBP buffering was attributable to sympathetic peripheral resistance control (multiplier S_{PR}); under pathological conditions this percentage was 78%. Also, 99% of the variance in BRS was attributable to vagal heart rate control (multiplier V); under pathological conditions this percentage was also 99%.

The scatter plot of the SBP buffering capacity as a function of S_{PR}, together with linear fits for the physiological and the pathological data (*Figure 3*, panel A), shows close to perfect linear relationships. Also, there is little difference between the linear fits for the physiological and the pathological simulation results. Obviously, heart rate control, but also the settings of V_{ref} and M_{PR} were of minor importance for blood pressure buffering.

The scatter plot of BRS as a function of V, together with linear fits for the physiological and the pathological data (*Figure 3*, panel B), shows nearly perfect linear relationships. Here, the physiological fit (slope 6.9 $ms \cdot mmHg^{-1}$) and the pathological fit (slope 4.0 $ms \cdot mmHg^{-1}$) differ considerably: with equal vagal gain multipliers, BRS is much larger in physiological conditions.

Figure 3 panel C shows that SBP buffering capacity and SBP resonance have a convex relationship and that the resonance phenomenon is much more prominent in physiological circumstances compared to pathological conditions. The strong link between buffering and resonance follows directly from regression analysis: also here, multiplier S_{PR} attributes the most to variance in SBP resonance (95% under normal conditions, 91% under pathological conditions).

Figure 3, panel D, finally, shows that BRS was almost unrelated to SBP buffering capacity, unless coupled baroreflex gains (simulation results represented by the open and solid squares) are assumed. The squared correlation coefficients of the linear regressions of SBP buffering capacity on BRS were as low as 0.037 (physiological conditions) and 0.083 (pathologic conditions).

DISCUSSION

We used a mathematical model to investigate the relation between baroreflex sensitivity (BRS, an index of baroreflex vigor) and baroreflex mediated blood pressure buffering capacity. This relation is not straightforward since the involved efferent baroreflex limbs (vagal and sympathetic pathways to the heart, and sympathetic pathways to the peripheral vasculature, respectively) differ. Moreover, baroreflex buffering occurs at lower frequencies than the Mayer frequency band in which BRS is noninvasively assessed and in which blood pressure resonates. Whether or not resonance disturbs the transfer function, thus precluding reliable BRS assessment in the Mayer frequency band is not known. Also it is not clear what the relation is between, on one hand, the 'desired' phenomenon of blood pressure buffering at frequencies lower than the Mayer frequency and, on the other hand, the phenomenon of blood pressure resonance in the Mayer frequency band (nothing more than a byproduct of baroreflex mediated blood pressure control[10]).

Simulations with various combinations of baroreflex gains, under physiologic as well as under pathologic conditions (increased sympathetic tone, decreased vagal tone, reduced cardiac stroke volume) yielded frequency characteristics of the transfer function, of HRV and of BPV, and values of BRS, blood pressure buffering capacity and baroreflex resonance in a wide range of conditions that may be met in real life. All frequency characteristics had a smooth character, and even with striking resonance the transfer function did not show discontinuous or deviant behavior when compared with its value below and above the frequency band of resonance (see *Figure 2*). In the following, the simulation results will be discussed in the order they have been presented in *Figure 3*.

Baroreflex gains and blood pressure buffering capacity

Our results suggest a predominant role for the sympathetic limb to the peripheral vasculature for the blood pressure buffering capacity of the arterial baroreflex (*Figure 3*, panel A). There is almost no difference in buffering capacity between the physiological and the pathological conditions. This result clearly illustrates the fact that efficacy of baroreflex mediated blood pressure control rests on dynamic control of the peripheral resistance. Modulation of heart rate by baroreflex mediated modulation of the vagal and sympathetic tone to the heart is not very relevant for blood pressure control in the frequency range of interest for this study (0.05 to 0.3 Hz).

Obviously, the simulation results may not be interpreted in such a way that baroreflex mediated blood pressure buffering in patients is not different from that in healthy subjects. The sympathetic feedback gain to the peripheral vasculature is the decisive factor here. We speculate that this gain will be lower in patients. Hence, it may have been somewhat unrealistic to extend the simulations in pathological conditions to a similar value of S_{PR} than the simulations in physiological conditions. The consequence of our speculation would be that the blood pressure buffering capacity in patients is smaller than that in healthy subjects.

Baroreflex gains and baroreflex sensitivity

BRS is linear with, and depends almost exclusively on the vagal feedback gain to the heart (*Figure 3*, panel B). The slopes of the linear regressions (6.9 and 4.0 ms·mmHg^{-1} with physiological and pathological conditions, respectively) are merely to be explained on the basis of heart rate differences between these two situations and the way the IPFM[18] reacts to fluctuations in vagal tone. The fact that BRS depends on heart rate has been recognized earlier[1] and proposals have been done to normalize BRS on heart rate, or, alternatively, to express BRS in [bpm·mmHg^{-1}] instead of in [ms·mmHg^{-1}]. Such arithmetic operations would change the linear relationships in *Figure 3* panel B in curved ones, but leave the conclusions unaffected that BRS increases with increasing vagal feedback gain and that the vagal feedback gain almost uniquely determines BRS.

The predominant role of the vagal feedback gain on the BRS[38] can also be formulated in a slightly different way: due to the differences in the time constants of the vagal and the sympathetic branches (in our model 0.1 s and 4.0 s, respectively), greater part of HRV is simply vagal transmission of blood pressure variability to the sinus node. This is easily perceived in panels B and C in *Figure 2* and in accordance with the findings of Cevese et al.[9]. When vagal feedback gain is zero (dotted lines in panels B) there is almost no HRV (panel B1) while there still is appreciable BPV (panel B2). When there is appreciable vagal baroreflex feedback gain (solid and dashed lines in panels B, and all lines in panels C) the HRV frequency characteristics in panels B1 and C1 have the same shape as the BPV frequency characteristics in panels B2 and C2. In the case of overt (sympathetically mediated) blood pressure resonance, where the BPV frequency characteristic has a narrow peak (panel C2), a similar 'monochrome' HRV frequency characteristic is seen in panel C1. Alternatively, when there is no outspoken resonance (panel B2), there is 'broad band' HRV (panel B1).

Blood pressure buffering capacity and Mayer waves

Figure 3 panel C illustrates the principle that a negative feedback control system with feedback delay buffers the controlled variable at certain frequencies at the cost of resonance at other frequencies. The baroreflex blood pressure control system as simulated in this study behaves in a way that is very similar to what was experimentally observed[10]. Blood pressure buffering, a major function of the baroreflex, occurs at frequencies below the Mayer waves (resonance in the LF band, *Figure 2* panel C2). Typically, the arterial baroreflex could dampen blood pressure and heart rate responses to stressors that last several minutes. On one hand, neural control of blood pressure by sympathetically induced vasoconstriction is relatively fast (seconds). On the other hand, baroreceptor resetting[47,50,51] limits the maximal duration during which baroreflex mediated buffering of a stressor may continue. In our simulations the BPV frequency characteristics in panels A2, B2 and C2 show that dampening (reduction of the sinusoidal pressure probe disturbance) is strongest for the lowest frequencies.

Although there still exist some controversy about the origin of the observed spontaneous blood pressure and heart rate variations around 0.1 Hz[32], we assume that this phenomenon is due to the dynamics of the closed-loop vasomotor control (arterial peripheral resistance), in which the time delay of a few seconds plays the major role. Building a baroreflex model with negative feedback control, and with parameters estimated from physiologically known data, results in a model that simply shows such resonance behavior, without the need to postulate centrally driven oscillators or (strong) nonlinearities.

Resonance, the price to be paid for buffering, is likely to be useless in terms of homeostasis. At the same time it may be an innocent phenomenon without any negative impact for the organism[22]. The fact that Mayer waves, useless or not, exist, facilitates spectral BRS assessment in the LF band, by creating an input signal (BPV) for the baroreflex of which the output signal (HRV) can easily be measured. There is no inherent signal analysis problem in measuring BRS by the transfer function around the resonance frequency. However, the 180° phase shift caused by the time lag in the sympathetic efferent baroreflex limb to the heart with respect to the phase shift in the efferent vagal limb, that has a much shorter time lag, may cause the sympathetic and vagal limbs to the heart to counteract in the LF band.

This effect will become prominent with

increased sympathetic gain to the heart (see, e.g., *Figure 2*, Panel A1, dashed line). In this respect, lower TF frequencies would constitute a more realistic BRS estimate, because here vagal and sympathetic feedback to the heart is concordant (Panel A3, dashed line). In general, TF values in the LF band are not too different at higher frequencies; TF values increase for lower frequencies (*Figure 2*, Panels A3, B3, C3).

Baroreflex sensitivity and blood pressure buffering capacity

One of the major reasons to perform this study was the question whether or not there is a relation between the primary function of the baroreflex, *i.e.*, blood pressure buffering, and the generally accepted clinical index for baroreflex vigor, BRS. *Figure 3*, panel D shows that this relation does almost not exist. The correlation coefficients of the regression lines of SBP buffering capacity on BRS are very low, and the data are diffusely distributed.

Indeed, vagal control of heart rate (major cause of the BPV-to-HRV transfer and, hence, major determinant of BRS) and sympathetic modulation of the peripheral vasculature (major cause of peripheral resistance adaptations and, hence, a major determinant of blood pressure buffering) become effective via separate efferent pathways of the baroreflex. There should not necessarily be a fixed relationship between the feedback gains in both reflex limbs[43].

To our knowledge, there are no data regarding the relative strength of the gains in the three baroreflex effector limbs. It might well be that subjects with a low gain in the vagal limb have also low gains in the sympathetic limbs, amongst others, because part of the origin of these gains is to be found in the common afferent pathway of the reflex starting at the baroreceptors in the arterial wall up to and including the nucleus tractus solitarii in the brainstem. Inspection of the simulation results obtained under coupled gains (closed and open squares in *Figure 3* panel D) reveals that in such cases there is a seemingly linear relationship between BRS and blood pressure buffering capacity in healthy subjects as well as in patients.

Limitations of the model

Basic to our study is the representativeness of the mathematical model. The original model has extensively been validated[46], amongst others by comparing the results of modeled vagal blockade and of standing with real world observations. The modified model, however, has a simplified hemodynamic structure. Since the simulations addressed blood pressure and heart rate control in the supine posture only, the dynamic control capabilities of cardiac contractility and venous return on cardiac output and hence, blood pressure, have completely been removed (obviously, such a simplification cannot be made in cases where the average IBI changes due to an altering circulatory load). Elimination of these feedforward mechanisms enabled us to concentrate on the role of the various baroreflex gains, especially in the LF-band, rather than steady state phenomena in the lower frequencies. As our simulation results are still comparable with the various spectra produced by the original model, we do believe that our model still produces relevant spectra.

The modified model that was used for our current study generates and explains some situations that are known from the clinic. It is obvious that the resonance phenomenon in the LF band, generally known as Mayer waves[33], is strongly under influence of the baroreflex. The only situations in which Mayer waves hardly appear is when the sympathetic baroreflex gain to the peripheral resistance is small (see *Figure 2*, panel C2, dotted line). This simulation result parallels studies in rats[19], and in humans[42,45]. The relevance of the model is underscored by the observation that SBP variability in the LF band decreases for fixed interval (results not shown here). This phenomenon was described by Taylor and Eckberg[45] in a study in humans. The authors demonstrated that baroreflex mediated heart rate control was not effective in reducing blood pressure variability, that had a larger amplitude in sinus rhythm compared with fixed-interval atrial pacing.

Within the operating space — constituted by the ranges of the parameters as given in *Table 1*, in combination with baroreflex gain multiplier values between 0 and 3 — our model can be used without any difficulty. For example, as the baroreflex gain to the peripheral resistance (S_{PR}) should not have any influence on the transfer function, *Figure 2* panel C3 shows indeed that only varying S_{PR} produce almost the same transfer functions. The minimal differences between those functions can be explained by nonlinearities in the model. Further expansion of the operating space may therefore be not allowed. Furthermore, higher baroreflex gains would no longer be realistic and leads to, e.g., unacceptably high BPV values.

BRS can be enhanced by training[7] and the beneficial effects of a thus increased BRS have convincingly been demonstrated[27]. How this effect is accomplished remains uncertain. Inhibition of stressor induced heart rate increases may be one reason; the vagal feedback gain in the cardiac efferent limb may predominantly cause this effect. Inhibition of stressor induced blood pressure increases may be another reason; the sympathetic feedback gain in the baroreflex efferent limb to the peripheral vasculature may predominantly cause this effect. Both effects could help to inhibit a stressor induced raise of myocardial oxygen consumption, which is proportional to the product of heart rate and systolic blood pressure[3,29].

A final remark regards the phenomenon as seen in *Figure 2*, panel A3. It appears that BRS (the TF between 0.05 and 0.15 Hz.) may lower with high sympathetic gain to the heart. This is caused by the differences in the latencies/time constants in the sympathetic[17,41] and vagal[6,48] limbs, bringing the vagal and the sympathetic effects in counterphase in the BRS frequency band. Hence, there are situations thinkable in which cancellation of vagal effects on heart rate by concurring sympathetic effects on heart rate in counterphase incorrectly suggest a deficient baroreflex. For higher frequencies, the influence of the sympathetic feedback gain weakens and disappears due to a low pass filtering effect caused by slow neurotransmitter diffusion at the synaptic clefts[17].

CONCLUSIONS

In conclusion, our simulation study suggests that, within the limitations of the model, BRS and baroreflex mediated blood pressure buffering are unrelated baroreflex features unless there is a good physiological reason to assume a fixed relation between the baroreflex feedback gains in the efferent baroreflex limbs to the heart and peripheral vasculature.

Also, we conclude that baroreflex mediated blood pressure buffering capacity is almost uniquely determined by the sympathetic baroreflex feedback gain to the peripheral vasculature, while BRS is almost uniquely determined by the vagal feedback gain to the sinus node.

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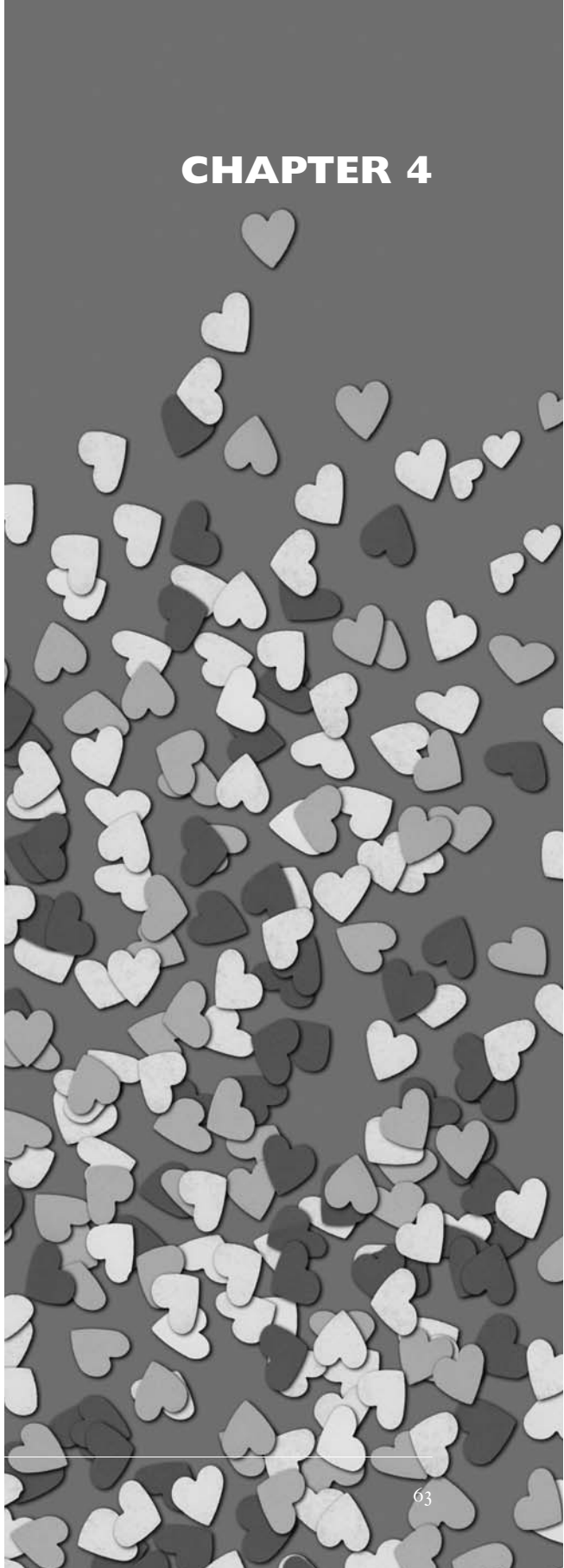
CHAPTER 4



PERIODIC SOMATOSENSORY STIMULATION INCREASES ARTERIAL BAROREFLEX SENSITIVITY IN CHRONIC HEART FAILURE PATIENTS

Submitted

ABSTRACT

Background. Exercise training induces major beneficial effects, e.g., in autonomic nervous system functioning. Arterial baroreflex sensitivity (BRS), an important prognostic marker in patients with chronic heart failure (CHF), is increased by exercise training, and it was demonstrated that exercise-induced BRS increase improves prognosis. The mechanism of this training effect is, however, unknown. We hypothesized that periodic somatosensory input to the brainstem is a training stimulus for the autonomic nervous system.

Methods. We compared in stable CHF patients the effect of transcutaneous electrical nerve stimulation (TENS, N=23, age 62 ± 12 years, LVEF 30 ± 9%) with the effects of bicycle exercise training (EXTR, N=20, age 59 ± 10 years, LVEF 32 ± 7%). To mimic exercise-associated somatosensory ergoreceptor stimulation, we applied periodic (2/s, marching pace) burst TENS to both feet. TENS and EXTR sessions were held during two successive days.

Results. BRS, measured noninvasively prior to the first intervention session and one day after the second intervention session, increased by 28% from 3.07 ± 2.06 to 4.24 ± 2.61 ms/mmHg in the TENS group, but did not change in the EXTR group (baseline: 3.37 ± 2.53 ms/mmHg; effect: 3.26 ± 2.54 ms/mmHg) (*P*(TENS vs EXTR) =0.02). Heart rate and systolic blood pressure did not change in either group.

Conclusions. We demonstrated that periodic somatosensory input alone is sufficient and efficient in increasing BRS in CHF patients. This concept constitutes a basis for new studies on more effective exercise training regimens in the diseased/impaired, in whom training aimed at BRS improvement should possibly focus more on the somatosensory aspect.

INTRODUCTION

Exercise training is effective in primary and secondary prevention. It induces major beneficial effects, e.g., in autonomic nervous system functioning. E.g., arterial baroreflex sensitivity (BRS), an important prognostic marker in chronic heart failure (CHF) patients[12,15], is increased by exercise training[20,25]. Patients with an exercise-induced BRS increase have, indeed, an improved life expectance[11]. Sadly, many patients with low BRS have limited exercise capacity. As a consequence, they cannot comply with the efforts that are deemed necessary for successful rehabilitation. Hence, insight in the currently unknown mechanism by which the training effect on BRS is mediated is of utmost importance. Possible hypothesis are:

Scenario 1:

CHF is characterized by permanent neurohumoral activation, i.e., elevated sympathetic tone, activation of the renin-angiotensin-aldosteron system and decreased BRS. Exercise training in CHF reduces sympathetic outflow and increases BRS[7]. Currently evidence suggests that these effects of exercise could be mediated by an NO-dependent GABAergic pathway in synergy with angiotensin II reduction[8,16].

Scenario 2:

On their way to the thalamus, neural fibres conveying ergoreceptor information form working muscle project to several structures, such as the nucleus tractus solitarii (NTS)[5]. During exercise, these projections release substance P at the NTS[22]. Substance P enhances BRS[18] by modulating the transmission of the baroreceptive afferents to the NTS neurons. Baroreflex enhancement after exercise may materialize in the NTS in the form of elevated substance P level that outlasts the exercise period[21,30]. We suppose that this effect lasts over 24 hours, which facilitates the development of a training effect with 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[17]. It is however not known if substance P has these long lasting effects in the NTS.

The consequence of the latter scenario would be that training effects in the baroreflex could be attained by exercise-mimicking somatosensory stimulation alone, without actual accompanying exercise. Therefore, we hypothesized that periodic somatosensory stimulation increases BRS.

METHODS

The local Medical Ethics Committees approved the study protocol. Eligible patients had CHF with systolic dysfunction and left ventricular ejection fraction (LVEF) <40%, were on stable medication and did not take part in any physical training program. All patients gave written informed consent. In the Leiden University Medical Center patients received somatosensory stimulation by means of transcutaneous electrical nerve stimulation (TENS group). As a control group we studied consecutive patients in Montescano scheduled for rehabilitation (EXTR group) who matched a TENS group subjects for age (within 5 years), heart rate (within 5 beats/min), LVEF (within 5%) and etiology (identical). Patient characteristics are presented in *Table 1*.

Table 1. *Patient characteristics.*

		TENS group	EXTR group
Sex		15M/8F	16M/4F
Age (years)		62 ± 12	59 ± 10
Heart rate		71 ± 10	69 ± 9
Systolic Blood Pressure (mmHg)		114 ± 17	108 ± 13
NYHA class I/II/III/IV		5/10/8/0	0/12/8/0
MLWHFQ		27 ± 17	27 ± 23
Etiology	Ischemic	13 (57%)	13 (65%)
	Non-ischemic	10 (43%)	7 (35%)
BMI (kg/m²)		25.6 ± 4.3	27.2 ± 5.1
LVEF (%)		30.3 ± 9.1	31.6 ± 6.6
Medication			
	ACE inhibitor/ AII blocker	20 (87%)	16 (80%)
	Diuretic	17 (74%)	16 (80%)
	Spironolactone	8 (35%)	5 (25%)
	Beta-blocker	17 (74%)	16 (80%)
	Amiodarone	6 (26%)	6 (30%)

Legend to Table 1. BMI: body mass index; LVEF: left ventricular ejection fraction; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association.

Sessions

Sessions were held on day 0 (baseline measurements followed by TENS or exercise training), day 1 (TENS or exercise training) and day 2 (effect measurements). For each patient these sessions were held at the same time of the day.

Measurements

During the measurements the patients were in supine position. To prevent respiratory discomfort, the upper part of the bed was inclined in accordance with individual sleeping habits. After 30 minutes of rest blood pressure and heart rate were measured with an automatic arm cuff blood pressure monitor (average of 5 subsequent readings), Then, the ECG and the noninvasive continuous arterial blood pressure signal (Finapres, TNO, Amsterdam, NL) were recorded during 10 minutes for later BRS calculation while patients performed 0.25 Hz metronome respiration (preventing the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency, 0.04-0.15 Hz, band in which we compute BRS[6]).

Experimental intervention: transcutaneous electrical nerve stimulation

Experimental intervention consisted of one hour TENS applied to both feet (*Figure 1*). To mimic locomotion/exercise-associated somatosensory ergoreceptor stimulation, we stimulated (Cefar Tempo TENS device, Cefar Medical AB, Lund, Sweden) both feet by peri-

odic (2/s, marching pace) bursts of 8 pulses (pulse width 180 μs, pulse rate 80 Hz). This electrical stimulus excites mainly A-δ nerve fibres[1], which carry ergoreceptor information and mediate cold, touch and sharp pain perception; A-α,β,γ and C fibers that mediate proprioception, motor activity, touch, pressure and deep pain sensation, and autonomic sympathetic control of the body tissues are less sensitive for this stimulus. To achieve the strongest possible stimulation without discomfort, the current was slowly increased until pain or muscle contractions occurred, and then reduced by 0.5 or 1.0 mA. To compensate for neuroadaptation, it was every 10 minutes attempted to increase the current. To reduce possible mental stress, all patients became acquainted with the TENS-induced sensations one week before session 0.

Exercise training

Exercise training consisted of the standard bicycle exercise protocol for cardiovascular patients. Patients treated with beta-blockers exercised at 75% of the heart rate reserve (reduced to 60% in case of limited exercise tolerance). Patients not treated with beta-blockers trained at similar levels unless the anaerobic threshold could be detected. In the latter case they exercised at the heart rate that corresponded to the anaerobic threshold (assessed by the V-slope method). Training consisted of: a) 2 minutes unloaded cycling; b) 3 minutes cycling at 50% of the endurance load; c) 30 minutes cycling at endurance load; d) 3 minutes cycling at 50% of the endurance load. Sessions were terminated if signs of distress (dizziness, angina, severe dyspnea or musculoskeletal pain) occurred.

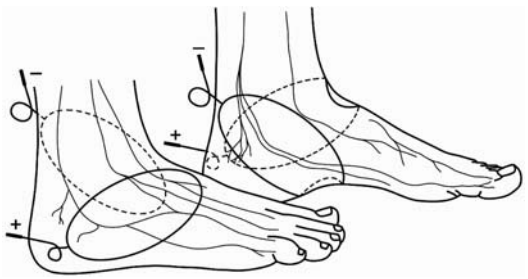


Figure 1. *Transcutaneous electrical nerve stimulation (TENS)*
Lateral and medial electrodes (4" foam-oval self-adhesive, AdvanTeq Development Corp, Thousand Oaks, CA, USA) cover branches of the peroneal and tibial nerves innervating the dorsal part and the heel/sole of the foot, respectively.

Baroreflex sensitivity calculation

All signals were blindly analyzed. First, all arrhythmia free and stationary periods >90 seconds in the metronome respiration episode were selected. Compliance to the metronome respiration protocol was visually verified in the respiration signal. Then, BRS was computed in each of the selected episodes. The BRS algorithm computes the magnitude of the transfer function between the systolic blood pressure (SBP) variability (baroreflex input) and the interbeat interval variability (output), averaged over the 0.04-0.15 Hz band. Additionally, it calculates 95% two-sided BRS confidence intervals (CI)[26]. Finally, the overall BRS was composed from all the BRS and CI values in data segments by the best linear unbiased estimator (BLUE) method[27].

Statistics

Data are expressed as mean ± SD. Baseline characteristics were evaluated by using unpaired two-sided t-tests, Mann-Whitney U tests and chi-square tests with Yates correction. Comparisons were done by t-tests for paired and unpaired data when appropriate.

RESULTS

Study groups

Twenty-three patients were enrolled in the TENS group and 20 in the EXTR group. The measured baseline characteristics of the control and exercise groups matched well (*Table 1*). Medication remained the same in all patients throughout the study.

Heart rate and systolic blood pressure

SBP values did not change after TENS, 114 ± 17 versus 115 ± 18 mmHg (P=0.45), nor after exercise training, 108 ± 13 versus 106 ± 10 mmHg (P=0.53). Also, after intervention, there was no significant change in resting heart rate in both groups, 70.8 ± 10.1 versus 68.6 ± 9.3 bpm in the TENS group (P=0.09), and 68.4 ± 9.2 versus 68.2 ± 7.9 bpm in the EXTR group (P=0.97).

Baroreflex sensitivity

BRS increased significantly with TENS compared to exercise training (P=0.02): in 18/23 (78%) of the subjects in the TENS group the effect BRS value was larger than baseline; BRS increased by 28% from 3.07 ± 2.06 to 4.2 ± 2.61 ms/mmHg (P=0.02). No significant change occurred in the EXTR group: baseline BRS value was 3.37 ± 2.53 ms/mmHg and the effect BRS value was 3.26 ± 2.54 ms/mmHg (P=0.90). Individual baseline and effect BRS values intervals are depicted in *Figure 2*.

DISCUSSION

Our study suggests that, in CHF patients, periodic somatosensory stimulation is sufficient and efficient in increasing BRS. This finding bears potential relevance for all patients with lowered exercise capacity and low BRS, as it supports the concept that, in such patients, low-intensity exercise training programs focusing on periodic somatosensory stimuli rather than on effort might induce the desired training effects.

Several studies have demonstrated the clinical value of BRS as a prognostic parameter[11,12,15]. Endurance training (and, in our study, TENS) improves BRS. Prognosis of patients in whom exercise increased BRS improved[11]. It is, however, not known how BRS improvement could induce the observed clinical effects; BRS improvement might be only an associated phenomenon. Recently, Ceroni and colleagues[3] addressed this issue with an experiment in which training effects were compared in sham operated and sino-aortic denervated rats. They concluded that the positive training effects,

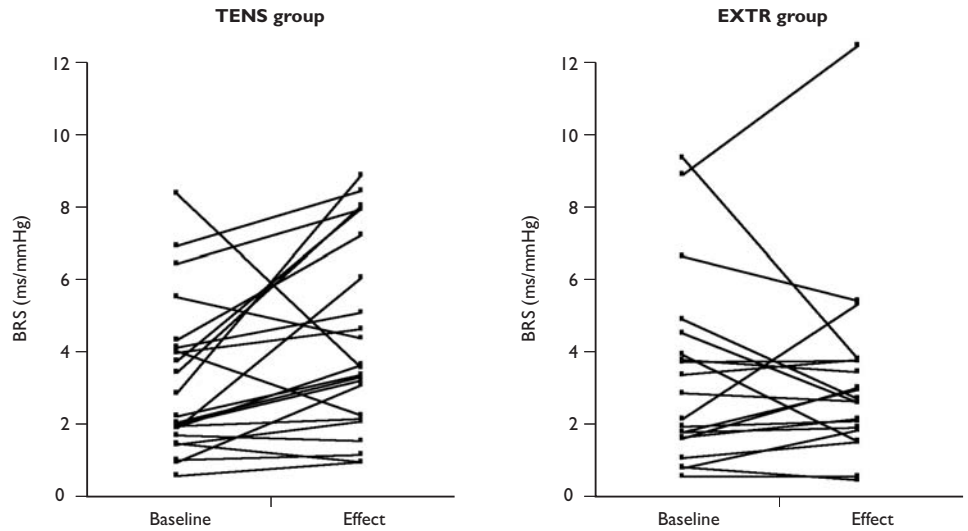


Figure 2. *Individual changes in baroreflex sensitivity (BRS)*
Individual BRS baseline and effect values in the TENS group (left panel) and the exercise training group (right panel). EXTR: *exercise training;* TENS: *transcutaneous electrical nerve stimulation.*

such as resting bradycardia and mean arterial pressure fall were only seen in animals with intact afferent baroreceptor information. When extending these results[3], we may assume that BRS improvement by any intervention removes a limiting factor for the emergence of beneficial training effects.

TENS increased BRS by 28%. In general, BRS changes may partly be explained by changes in resting heart rate and SBP, however, we found that both heart rate and SBP did not change after intervention. This makes the concept tenable that periodic afferent somatosensory nerve traffic caused the observed BRS increase. This effect differed significantly from the negligibly small BRS change in the EXTR group. To our knowledge, no studies in CHF patients have been conducted in which BRS changes after one or a few exercise sessions were measured. Such a quick effect cannot be outruled. Convertino and Adams showed that one bout of exercise was sufficient in inducing an observable 24 hours BRS increase[4]. However, this study was done in healthy men and with exhaustive exercise, while the maximal exercise level in CHF patients is much lower and the exercise intensity in our study was 75% of the heart rate reserve.

The training effect (28% BRS increase) after only two days of TENS was about half of the effect observed in much longer exercise programs[11,20]. The quickly achieved effect could be explained by the much stronger somatosensory stimulus generated by TENS than by the low intensity cycling in CHF training. If strong somatosensory stimuli are truly that important, the more discrete sensations that accompany walking might even be superior to cycling as a baroreflex training stimulus, even when this occurs at lower exercise intensity. E.g., the value of brisk walking for the prevention of cardiovascular events in postmenopausal women has convincingly been demonstrated[13].

When ergoreceptors are chronically firing, which happens when chemoreceptors are becoming stimulated due to metabolic processes in working muscle the projections of ergoreceptor-associated fibers to the rostral ventrolateral medulla[23] increase sympathetic outflow[24]. This is a stressing condition as it elevates SBP and heart rate[10]. The experimental 'training stimulus' rather mimics the periodic, intermittent mechanoreceptor stimulation in active muscle[21]. It is known that periodic ergoreceptor-associated stimulation of higher centers[5] activates the hypothalamic endorphinergic system[1]. The descending serotinergic projections of this system to the rostral ventrolateral medulla limits sympathetic outflow.

We choose the feet a stimulation site because of their involvement in most exercise modalities (hence, a 'natural' place to stimulate when attempting to mimic somatosensory nerve traffic during exercise), because they are distant from the heart and therefore safe[2], and because stimulation is relatively easy as the peroneal and tibial nerve branches in the feet run very superficially. It is conceivable that similar electrical stimuli, applied at different sites and exciting A-δ nerve fibres, will also increase BRS. Hence, there is no explicit reason why the NTS would process somatosensory information from, e.g., the hands, different that from the feet. Further experimentation is required to explore this.

To our knowledge, no earlier attempts to achieve a training effect in BRS by periodic somatosensory stimulation were done. Wang and Yao published the first evidence, in rabbits, that the baroreflex may be altered by electroacupuncture or deep peroneal nerve stimulation[29]. Later, other animal studies confirmed and explained these effects[14,21]. However, these studies all addressed baroreflex functioning during stimulation rather than with a delay after intervention, what is needed to demonstrate a training effect.

With our study, we have not aimed to test TENS as a therapeutic alternative for exercise training to improve BRS in CHF. We rather used TENS to provide the proof-of-the-principle by fully separating periodic somatosensory stimulation and exercise. Obviously, in clinical practice, actual exercise is to be preferred, as besides increasing BRS, is also induces other major peripheral beneficial effects[19]. It has to be realized that the somatosensory afferent information during exercise is more complex than the relatively simple artificial electrical stimulus used in our study. Hence, it has still to be proven that the rhythmic/periodic component in somatosensory nerve traffic during exercise is important or even crucial to achieve BRS training effects. A more pragmatic approach would be the design and validation of novel experimental exercise programs focusing on rhythmicity/periodicity rather than on effort. If proven effective, 'autonomic fitness' (a good working baroreflex) might thus be achievable for large groups of exercise-deprived or exercise-limited persons.

Limitations

Several limitations of our study need attention. First, our study was not randomized, however, the measured baseline characteristics of both groups matched well (*Table 1*).

Second, our study did not directly address the supposed mechanism of BRS improvement due to periodic somatosensory stimulation. Animal studies are needed to reveal what happens at the level of the brainstem. In humans, muscle sympathetic nerve activity recordings could reveal if there is an effect of periodic somatosensory stimulation on the sympathetic baroreflex gain[9] (BRS measurements cannot discern between parasympathetic and sympathetic baroreflex gain[28]).

Third, we did not include a group receiving "placebo TENS", which limits the validity of our results. Placebo TENS would, e.g., involve subthreshold stimulation. According to the Convention of Helsinki, research protocols with humans require complete information of candidate participants, hence, whatever the placebo stimulation would be, fully informed participants would know the difference between the placebo and the experimental stimulus. Hence, equal trust/mistrust in the experimental and placebo treatments, a prerequisite for a good placebo, cannot be attained. Instead, we decided to contrast TENS with the conventional intervention of exercise training, which, admittedly, does not fulfill the methodological requirements of a real placebo treatment.

CONCLUSIONS

In conclusion, periodic somatosensory stimulation to the feet is potentially able to increase BRS in CHF patients. This finding is an opening to more comprehensive trials to evaluate exercise modes that focus mainly on rhythmic/periodic somatosensory stimuli. Also, follow-up studies are needed to corroborate our findings in larger groups of persons with varying pathology, to establish the mechanism, and to assess the associated health benefits.

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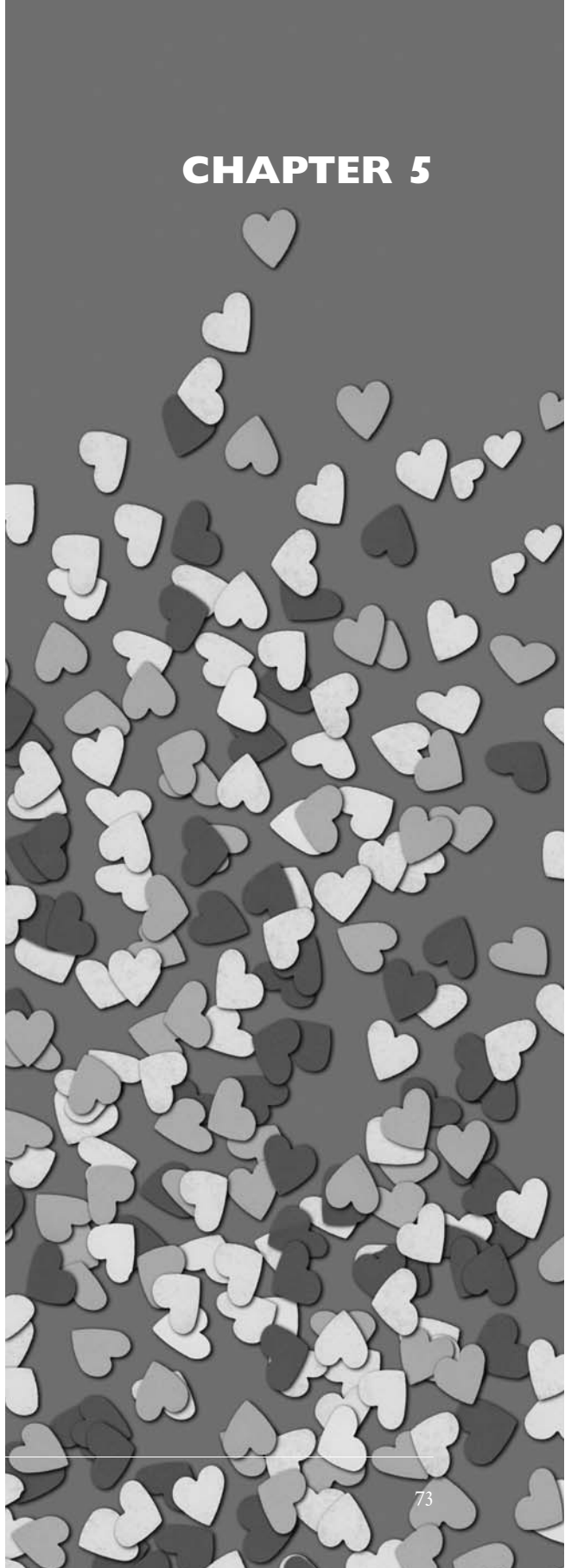
CHAPTER 5

EXERCISE TRAINING INCREASES OXYGEN UPTAKE EFFICIENCY SLOPE IN CHRONIC HEART FAILURE

Eur J Cardiovasc Prev Rehabil 2007;15:140-144



ABSTRACT

Background and Aim. The oxygen uptake efficiency slope (OUES) is a novel measure of cardiopulmonary reserve. OUES is measured during an exercise test, but it is independent of the maximally achieved exercise intensity. It has a higher prognostic value in chronic heart failure (CHF) than other exercise-test derived variables like $\dot{V}O_{2\,peak}$ or $\dot{V}E/\dot{V}CO_2$ slope. Exercise training improves $\dot{V}O_{2\,peak}$ and $\dot{V}E/\dot{V}CO_2$ in CHF patients. We hypothesized that exercise training also improves OUES.

Methods and Results. We studied 34 New York Heart Association (NYHA) class II-III CHF patients who constituted an exercise training group T (N= 20; 19 men/1 woman; age 60 ± 9 years; left ventricular ejection fraction 34 ± 5%) and a control group C (N=14; 13 men /1 woman; age 63 ± 10 years; left ventricular ejection fraction 34 ± 7%). A symptom-limited exercise test was done at baseline and repeated after four weeks (C) or after completion of the training program (T). Exercise training increased NYHA class from 2.6 to 2.0 (P<0.05), $\dot{V}O_{2\,peak}$ by 14% (P(TvsC)<0.01), and OUES by 19% (P(TvsC)<0.01). Exercise training decreased $\dot{V}E/\dot{V}CO_2$ by 14% (P(TvsC)<0.05).

Conclusion. Exercise training improved NYHA class, $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$ and also OUES. This finding is of great potential interest as OUES is insensitive for peak load. Follow-up studies are needed to demonstrate wether OUES improvements induced by exercise training are associated with improved prognosis.

INTRODUCTION

Cardiopulmonary performance is often assessed by maximal oxygen uptake ($\dot{V}O_{2\,max}$). Basically, $\dot{V}O_{2\,max}$ is an objective parameter, that is defined as the point at which oxygen uptake reaches a plateau despite continuing exercise and increasing workload[25]. Unfortunately, such a plateau is often difficult to perceive[14], and in symptom-limited exercise tests, as performed in chronic heart failure (CHF), the plateau is often not attained[24]. Hence, in practice, peak oxygen uptake ($\dot{V}O_{2\,peak}$) is assessed in CHF patients instead of $\dot{V}O_{2\,max}$[15]. Obviously $\dot{V}O_{2\,peak}$ is strongly influenced by the motivation of the patient, the selected exercise protocol and the tester's subjective choice of the test end point[1,22].

As a result of these drawbacks, Baba et al.[2] have introduced the oxygen uptake efficiency slope (OUES), an objective and reproducible measure of cardiopulmonary function reserve that can also be measured with submaximal exercise[4,12,27]. In CHF patients it was shown that among other exercise-test derived parameters ($\dot{V}O_{2\,peak}$; ventilatory response to exercise –$\dot{V}E/\dot{V}CO_2$–; ventilatory anaerobic threshold –VAT–) OUES had the strongest prognostic value; OUES was also the only parameter with independent prognostic value[6]. It is known that exercise training improves $\dot{V}O_{2\,peak}$ and $\dot{V}E/\dot{V}CO_2$ in CHF patients9[19,21], however convincing proof that exercise training also increases OUES in CHF patients has not been published yet. There certainly are positive indicators that this might be the case: exercise training improves OUES in other patient groups (coronary artery disease, haemodialysis[7,26]) and Van Laethem et al.[13] recently published, in an uncontrolled study, suggestive evidence that exercise training also increases OUES in CHF patients. Our current study aims to complete this evidence by using a controlled protocol.

METHODS

Patients

The Medical Ethics Committees of the Leiden University Medical Centre and of the Rijnland Rehabilitation Center approved the protocol of this study. The investigation conforms with the principles outlined in the Declaration of Helsinki[20]. All participants gave written informed consent. Eligible patients had CHF New York Heart Association (NYHA) class II or III, with systolic dysfunction and a left ventricular ejection fraction (LVEF) less than 45%. Patients with pulmonary hypertension and chronic obstructive pulmonary disease were excluded from the study.

Two groups of patients, a sedentary control group and an exercise training group, were defined as follows. Consecutive CHF patients who had one regular baseline symptom-limited exercise test before commencing their actual rehabilitation program, and in whom a final evaluative symptom-limited exercise test was performed 1 day after completing the last training session, constituted the training group. After inclusion of the exercise training group, we started inclusion of the control group. For this group, consecutive patients eligible for rehabilitation were selected who matched one of the participants of the training group for age (within 5 years), NYHA class (identical), LVEF (within 5%) and etiology (identical). The patients in the control group had 2 baseline symptom-limited exercise tests, 4 weeks apart, before starting their actual rehabilitation program. *Table 1* summarizes the main patient characteristics of the training and control groups.

Symptom-limited exercise testing

Symptom-limited exercise tests at baseline and after 4 weeks (control group) or after completion of the rehabilitation program (training group) were done with respiratory gas exchange analysis (Oxycon Pro, Jaeger-Viasys Healthcare, Hoechberg, Germany). Exercise intensity started at 5 Watts and was increased by 5 Watts every 30 seconds. Participants exercised to their self-determined maximal capacity or until the supervising physician stopped the test because of significant symptoms, such as

Table 1. *Patient characteristics.*

		Training group	Control group	*P*-value
Sex		19M / 1F	13M / 1F	NS
Age (years)		60 ± 9	63 ± 10	NS
LVEF (%)		34 ± 5	34 ± 7	NS
BMI (kg/m²)		27.3 ± 3.5	28.7 ± 3.0	NS
NYHA class		2.6 ± 0.5	2.3 ± 0.4	NS
Etiology				
	Ischemic	11 (55%)	6 (43%)	NS
	Non-ischemic	9 (45%)	7 (57%)	NS
Medication				
	Antithrombotic therapy	16 (80%)	11 (79%)	NS
	ACE inhibitor/AII blocker	18 (90%)	14 (100%)	NS
	Diuretic	12 (60%)	10 (71%)	NS
	Spironolactone	3 (15%)	4 (29%)	NS
	Beta-blocker	17 (85%)	12 (86%)	NS
	Statin	14 (70%)	10 (71%)	NS
	Digoxin	0 (0%)	0 (0%)	NS
	Amiodarone	4 (20%)	1 (7%)	NS

Legend to Table 1. BMI: body mass index (kg · m^{-2}); F: female; LVEF: left ventricular ejection fraction; M: male; NS: not significant (P>0.05); NYHA: New York Heart Association functional class.

chest pain, dizziness, potentially dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension. Breath-by-breath respiratory gas analyses were performed throughout the entire test. $\dot{V}O_2$ values were determined over every 30 second period, and over the terminating measurement period at peak exercise when this was more than 15 seconds long. The last valid $\dot{V}O_2$ value was taken as $\dot{V}O_{2\,peak}$.

$\dot{V}E/\dot{V}CO_2$ slope and OUES calculation

$\dot{V}E/\dot{V}CO_2$ slope was obtained by linear regression analyses of the relation between $\dot{V}E$ and $\dot{V}CO_2$ during the entire symptom-limited exercise test.

OUES was computed by a linear least squares regression from the oxygen uptake on the logarithm of the minute ventilation ($\dot{V}E$) according to the following equation: $\dot{V}O_2 = \mathbf{a} \cdot \log_{10}\dot{V}E + \mathbf{b}$. Constant **a** is called the oxygen uptake efficiency slope (OUES), as it represents the rate of increase in oxygen uptake in response to a change in minute ventilation[2]. In order to assess the validity of OUES during a submaximal exercise test, OUES was also calculated from data derived form the first 75% (OUES75) and 90% (OUES90) of the entire exercise duration.

To compare the OUES results from our study group with reference values, we computed the predicted OUES for age, body surface area (BSA) and sex-matched normal participants according to the equations published by Hollenberg et al.[12]: for women, OUES = 1175 – 15.8·age + 841·BSA; for men, OUES = 1320 – 26.7·age + 1,394·BSA.

Exercise training

Patients in the training group attended 30 exercise training sessions. Training sessions were conducted 2 to 3 times a week, lasted about 75 minutes and consisted of 20 minutes cycling, starting at 50% of the maximal load attained during the baseline symptom-limited exercise test, preceded/followed by warming up/cooling down. Per session, this load was increased, until the attained heart rate was equal to the heart rate at the anearobic threshold as estimated during the baseline test. Further endurance exercise during 15 minutes was *ad libitum* and consisted of rowing or walking. Additionally, all patients in the training group conducted light resistance training, consisting of 1 series of 25 repetitions of each of the following exercises; flies, rowing, chest press, shoulder press, leg extension, leg curl, leg press and pull down. Intensity was chosen and, in the course of the training program, adjusted in such a way that the patient experienced nearly complete exhaustion of the involved muscle group after 25 repetitions.

Statistics

The statistical data are expressed as mean ± SD. Baseline characteristics were evaluated by using Mann-Whitney U-test and chi-square tests, Yates correction was used. A Mann-Whitney U-test were used to compare, between the training and the control group, baseline values, and individual changes in $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$, OUES/kg, OUES, OUES90 and OUES75. A paired Student's *t*-test was used to compare the measured OUES with the reference OUES. NYHA functional class within the training group changes were evaluated with a Wilcoxon signed-rank test. Differences in OUES75, OUES90 and OUES of the entire maximal exercise duration were assessed by a repeated-measures analysis of variance.

RESULTS

Patient characteristics

No significant differences were found for sex, age, LVEF, body mass index, NYHA functional class, etiology and medication of the training and the control group (*Table 1*). Throughout the study, the type and dose of medications remained the same for all patients.

Oxygen consumption

Baseline $\dot{V}O_{2\,peak}$ values of the training and the control groups did not differ significantly; exercise training increased $\dot{V}O_{2\,peak}$ by 14%, this was significantly different ($P<0.01$) from the change in the control group (*Table 2*).

$\dot{V}E/\dot{V}CO_2$ slope

As expected the $\dot{V}E/\dot{V}CO_2$ slope was elevated, both groups exceed the upper normal limit of 30[5] (*Table 2*). Baseline $\dot{V}E/\dot{V}CO_2$ slope values of the training and the control groups did not differ significantly; exercise training decreased $\dot{V}E/\dot{V}CO_2$ slope by 14%. This difference was significantly different ($P<0.01$) compared with the insignificant change in the control group (*Table 2*).

Oxygen uptake efficiency

Baseline OUES and OUES/kg values of the training and the control groups did not differ significantly; exercise training increased OUES by 19% and OUES/kg by 17% (*Table 2*). This increase differed significantly ($P<0.001$) from the change in the control group (*Table 2*).

As expected, OUES75 and OUES90 did not differ relevantly from OUES (*Fig 1*), OUES75 underestimated OUES by 1.4% and OUES90 overestimated OUES by 0.5%. As there was no significant difference in the beginning in the analysis of variance repeated measures (Greenhouse-Geisser *P* value was 0.09), there was no need to correct for multiple comparisons. Exercise training increased OUES75 significantly by 21%

Table 2. *Changes in* $\dot{V}O_{2\,peak}$ *and* OUES.

	Group	Baseline	Remeasurement	Change (%)	P_{BvsR}
OUES/kg	Control	20.2 ± 4.7	21.2 ± 5.7	5	NS
[(ml O2/min)/(L VE/min)]	Training	19.8 ± 5.1	23.2 ± 4.8	17	<0.001
P_{CvsT}		NS	<0.001*		
OUES	Control	1763 ± 362	1854 ± 451	5	NS
[(ml O2/min)/(L VE/min)]	Training	1690 ± 447	2017 ± 462	19	<0.001
P_{CvsT}		NS	<0.001*		
OUES90	Control	1792 ± 335	1903 ± 443	6	NS
[(ml O2/min)/(L VE/min)]	Training	1660 ± 470	2030 ± 436	22	<0.001
P_{CvsT}		NS	<0.001*		
OUES75	Control	1797 ± 324	1923 ± 440	7	NS
[(ml O2/min)/(L VE/min)]	Training	1609 ± 388	2010 ± 406	21	<0.001
P_{CvsT}		NS	<0.001*		
VE/VCO2slope	Control	35.5 ± 3.6	35.8 ± 3.9	0	NS
	Training	35.8 ± 9.6	31.0 ± 6.1	14	<0.01
P_{CvsT}		NS	<0.05*		
$\dot{V}O_{2\,peak}$	Control	17.1 ± 3.5	16.9 ± 3.9	–1	NS
(ml O2/kg/min)	Training	16.9 ± 4.4	19.4 ± 4.9	14	<0.01
P_{CvsT}		NS	<0.05*		

Legend toTable 2. CvsT: control group *vs.* training group; BvsR: baseline *vs.* remeasurement; NA: not applicable; NS: not significant; OUES: oxygen uptake efficiency slope (constant **a** in equation $\dot{V}O_2 = \mathbf{a} \cdot \log \dot{V}E + \mathbf{b}$); OUES75: OUES calculated from data derived form the first 90% of the symptom limited exercise test; OUES90: OUES calculated from data derived form the first 90% of the symptom limited exercise test; $\dot{V}O_{2\,peak}$: peak oxygen uptake [ml O_2/kg/min]; *: *P*-values for the difference between the change in parameters.

and OUES90 by 22%. Again there was no significant change in the control group (*Table 2*).

OUES assessed in the control group and in the training group were significantly lower (71% and 67% respectively) than reference OUES values for matched normal subjects (*Table 3*).

New York Heart Association functional class

Baseline NYHA functional class of the training and the control groups did not differ significantly. After the exercise training program, 10 patients improved one NYHA functional class and 1 patient improved two NYHA functional classes ($P<0.01$).

DISCUSSION

As compared to normal values, baseline $\dot{V}O_{2\,peak}$ and OUES were depressed, baseline $\dot{V}E/\dot{V}CO_2$ slope was increased. According to expectation[19], exercise training increased $\dot{V}O_{2\,peak}$ and decreased $\dot{V}E/\dot{V}CO_2$ slope. The control group showed an increasing trend of OUES, probably caused by a familiarization effect. Nevertheless, the increase of OUES in the exercise group differed significantly from the change in the control group. Therefore, our study confirmed our hypothesis that exercise training increases OUES in CHF patients. To our knowledge, this is the first controlled study that reports a beneficial effect of exercise training on OUES in CHF. This finding is of great potential interest. Multiple factors affect the maximal load attained during a symptom-limited maximal exercise test[1,22]. As a consequence, individual $\dot{V}O_{2\,peak}$ values are relatively unreliable. Contrastingly, we found, in line with the findings by Hollenberg et al.[12] and van Laethem et al.[27], that OUES is a more consistent parameter. Hence, OUES75 and OUES90 also increased significantly in the exercise training group.

Physiological background of the oxygen uptake efficiency slope

OUES was significantly lower than the computed OUES reference values. Factors affecting OUES are the arterial carbon dioxide set point (P_ACO_2), the metabolic carbon dioxide production ($\dot{V}CO_2$) and the ratio of pulmonary dead space to tidal volume (Vd/Vt)[2]. During exercise, the arterial carbon dioxide set point in CHF patients does not differ from normal[23]. Metabolic acidosis in CHF patients, however, occurs at lower workloads than in healthy persons as a consequence of reduced muscle perfusion and structural muscular changes[17]. This causes increased ventilation[18]. Moreover, the reduced lung perfusion in CHF patients results in an increase in the physiologic pulmonary dead space[2]. Hence, a depressed OUES in CHF patients is likely resulting from underperfusion of skeletal muscle and underperfusion of the lungs. The observed exercise training-induced increase in OUES is therefore presumably attributable to both peripheral muscular adaptations, such as increased capillary density, blood flow, mitochondrial volume density, fibre size, slow twitch fibres and decreased lactic acidosis and vascular resistance[8,10,11,16], and pulmonary adaptations like increased alveolar capillary membrane perfusion and capillary blood flow[9]. In accordance with this, the decrease in $\dot{V}E/\dot{V}CO_2$ slope indicates decreased lactic acidosis and a better ventilation/perfusion match in the lungs.

Table 3. *Assessed versus predicted* OUES.

Group	Assessed OUES [(ml O2/min)/(L VE/min)]	Predicted OUES [(ml O2/min)/(L VE/min)]	% predicted OUES [(ml O2/min)/(L VE/min)]	$P_{assessed\ vs\ predicted}$
Training group	1690 ± 447	2542 ± 355	67	<0.001
Control group	1763 ± 362	2497 ± 396	71	<0.001

Legend to Table 3. OUES: oxygen uptake efficiency slope (constant **a** in equation $\dot{V}O_2 = \mathbf{a} \cdot \log \dot{V}E + \mathbf{b}$).

Limitations

Although our study was not randomized, the baseline characteristics of the control and exercise groups matched reasonably well (*Table 1*). Moreover, although the duration between the two exercise tests in the control group is probably not of great importance, it is a limitation that there was a discrepancy in the time between the initial and the second exercise test between the two groups.

Whether similar results (more specifically, a significant increase of OUES in the training group) would have been obtained with other exercise training modalities (e.g., walking/running instead of endurance cycling) or with other exercise testing modalities (e.g., treadmill vs. cycle ergometry) cannot be answered with our current data. So far, standard exercise testing protocol has been defined for OUES assessment, and OUES is currently being measured with treadmill as well as with cycle ergometry[2,4,6,7,27]. Baba et al.[3] have shown that there was excellent intra-individual agreement between OUES values measured with two different treadmill protocols. Hence, OUES seems to be relatively insensitive to the testing protocol, and it is not very likely that the results of our study would have differed very much when treadmill instead of cycle ergometry had been used.

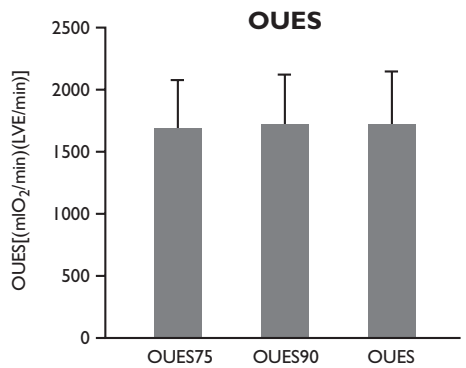


Figure 1. *Effect of shortened exercise duration on* OUES. OUES*: oxygen uptake efficiency slope;* OUES75*:* OUES *calculated from data derived form the first 75% of the symptom limited exercise test;* OUES90*:* OUES *calculated from data derived form the first 90% of the symptom limited exercise test.*

CONCLUSIONS

In conclusion, our study demonstrates that exercise training in CHF patients increases OUES, a robust parameter for cardiorespiratory reserve with a strong independent prognostic value in heart failure. This positive training effect is associated with an improvement in the NYHA functional class and other cardiorespiratory parameters. Follow-up studies are needed to determine whether an increase of OUES in a heart failure patient is associated with improved prognosis.

ACKNOWLEDGEMENTS

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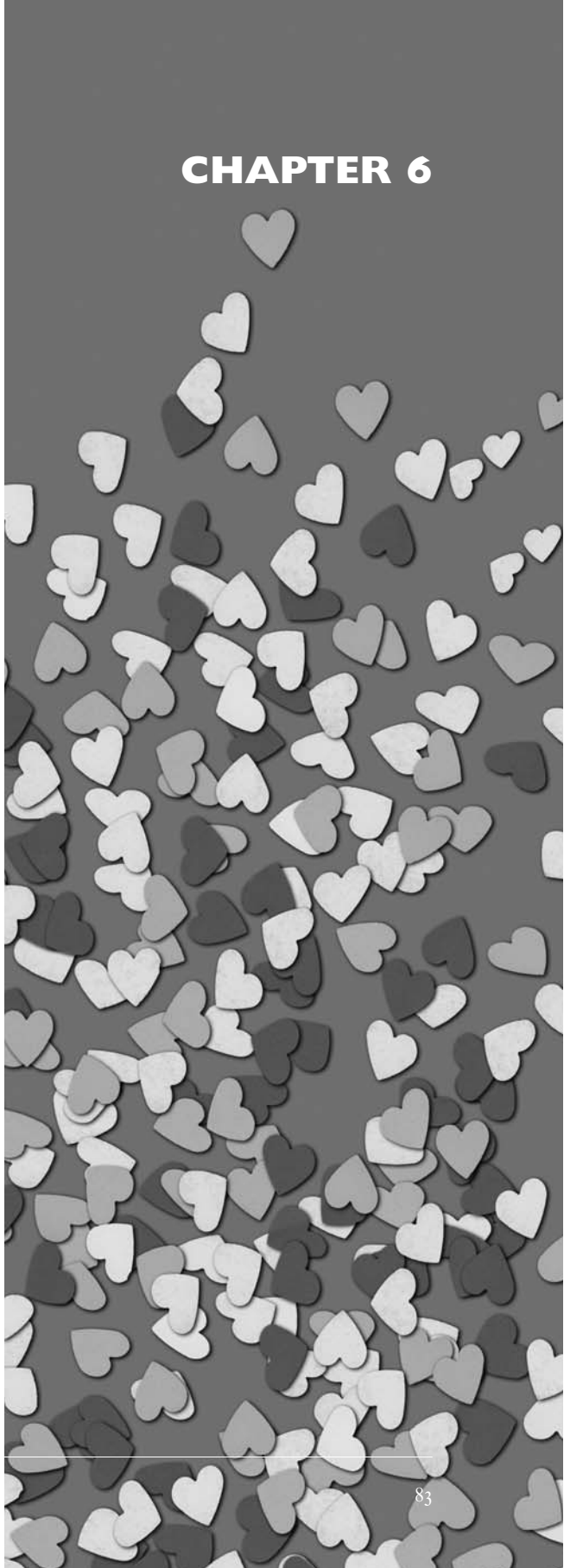
CHAPTER 6



THE EFFECT OF EXERCISE TRAINING ON THE OXYGEN UPTAKE-WORK RELATION IN CHRONIC HEART FAILURE

Submitted

ABSTRACT

Background. The oxygen uptake-work relation ($\Delta\dot{V}O_2/\Delta W$) has predictive value in chronic heart failure (CHF) and the reduction in $\Delta\dot{V}O_2/\Delta W$ reflects the severity of this disease. Exercise training improves prognosis in CHF patients. Exercise training also improves several cardiopulmonary exercise testing variables in these patients. It is, however, unknown if exercise training improves $\Delta\dot{V}O_2/\Delta W$ in CHF. We hypothesized that exercise training improves $\Delta\dot{V}O_2/\Delta W$ in CHF patients with subnormal $\Delta\dot{V}O_2/\Delta W$.

Methods. We studied 36 New York Heart Association (NYHA) class II-III CHF patients, randomized into an exercise training group T (N=18; 15M/3F; age 60 ± 11 yrs; LVEF 32 ± 7%) and a control group C (N=18; 17M/1F; age 63 ± 9 yrs; LVEF 33 ± 7%). A progressive workload exercise test was done at baseline and repeated after four weeks (group C) or after completion of the training program (group T).

Results. Exercise training improved $\dot{V}O_{2\,peak}$ by 23% (P(TvsC)<0.0001), OUES by 18% (P(TvsC)<0.01), W_{max} by 17% (P(TvsC)<0.01) and $\dot{V}E/\dot{V}CO_2$ slope by 10% (P(TvsC)<0.02). Exercise training did not improve $\Delta\dot{V}O_2/\Delta W$ (P(TvsC)= 0.86). However, 33% of T and 50% of C had a relatively normal $\Delta\dot{V}O_2/\Delta W$ (>10 (ml/min)/Watt) at baseline. $\Delta\dot{V}O_2/\Delta W$ improved in the population with subnormal baseline $\Delta\dot{V}O_2/\Delta W$ values from 8.71 ± 0.90 to 9.14 ± 0.78 (ml/min)/Watt (P(TvsC)= 0.04).

Conclusions. Exercise training improved $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$, W_{max}, and OUES. In patients with subnormal $\Delta\dot{V}O_2/\Delta W$ exercise training improved $\Delta\dot{V}O_2/\Delta W$. Further research has to reveal the prognostic significance of exercise-induced $\Delta\dot{V}O_2/\Delta W$ improvements.

INTRODUCTION

The oxygen uptake-work rate relation ($\Delta\dot{V}O_2/\Delta W$) describes the amount of oxygen that is utilized in relation to the amount of external work performed. $\Delta\dot{V}O_2/\Delta W$ has important prognostic power in chronic heart failure (CHF)[20]. While patients with mild CHF have sometimes relatively normal $\Delta\dot{V}O_2/\Delta W$ values[17,29], $\Delta\dot{V}O_2/\Delta W$ is often subnormal in CHF, and the amount of depression reflects the severity of CHF. The mechanisms that lower $\Delta\dot{V}O_2/\Delta W$ in CHF are not fully understood, most likely this is to be attributed to the attenuated cardiac output response to exercise[31] and to other components of oxygen delivery and utilization systems, e.g., pulmonary, vascular and skeletal muscle systems[1,15].

Exercise training therapy is effective in CHF: it lessens dyspnea and fatigue[12,21], improves quality of life, improves New York Heart Association (NYHA) class[2,4,22], decreases morbidity, and may even decrease mortality[24,26]. Also, several cardiopulmonary exercise-testing variables like $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$ slope and OUES increase with exercise training[9,33]. Whether exercise training also improves $\Delta\dot{V}O_2/\Delta W$ is unknown.

Exercise training may well improve factors that caused a decrease in $\Delta\dot{V}O_2/\Delta W$, such as cardiac output and pulmonary, vascular and skeletal muscle systems. Studies report an improvement in intrinsic skeletal muscle properties[11,13,25], a decrease in tissue inflammation[10], a decrease in the concentration of vasoconstrictive agents[5,6,12] and an improvement of endothelial function[23,28]. Hence, we hypothesized that in CHF patients with subnormal $\Delta\dot{V}O_2/\Delta W$ values, exercise training also improves $\Delta\dot{V}O_2/\Delta W$.

METHODS

Patients

Our institutional Medical Ethics Committees approved the protocol of this study. All participants gave written informed consent. Eligible patients (NYHA class II or III CHF with systolic dysfunction and left ventricular ejection fraction < 45%) were scheduled for cardiopulmonary rehabilitation. Patients with pulmonary hypertension and/or chronic obstructive pulmonary disease were excluded from the study.

Patients were randomized to a control (C) and an exercise training group (T). T patients performed exercise tests before commencing their exercise training program and within one week after their final training session. C patients performed two exercise tests, four weeks apart, before starting their actual training program.

Exercise testing

The symptom-limited exercise tests were done with respiratory gas exchange analysis (Oxycon Pro, Jaeger). Exercise intensity started at 5 Watts and was increased by 5 Watts every 30 seconds. Maximal work rate (W_{max}) was defined as the highest obtained workload minimally maintained for 30 seconds. Subjects exercised to their self-determined maximal capacity or until the supervising physician stopped the test because of adverse symptoms, e.g., chest pain, dizziness, potentially dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension. Breath-by-breath respiratory gas analysis was done throughout the entire test.

Exercise testing variables

Oxygen uptake ($\dot{V}O_2$) values were determined over every 30 second period and over the final measurement period at peak exercise when this was more than 15 seconds long. The last valid $\dot{V}O_2$ value was taken as peak $\dot{V}O_2$ ($\dot{V}O_{2\,peak}$). $\Delta\dot{V}O_2/\Delta W$ was calculated by linear regression of $\dot{V}O_2$ on work rate, from 1 minute after the beginning to 80% of the total exercise test duration[32]. $\dot{V}E/\dot{V}CO_2$ slope was obtained by linear regression of minute ventilation ($\dot{V}E$) on carbon dioxide output ($\dot{V}CO_2$) over the entire exercise test. OUES was computed by a linear least squares regression from $\dot{V}O_2$ on the logarithm of the minute ventilation ($\dot{V}E$) over the entire exercise test[3].

Exercise training

T-patients performed 30 exercise training sessions, which were held 2 to 3 times a week. The initial 20 minutes of a training session consisted of cycling. Exercise intensity during the first session was 50% of the maximal load attained during the baseline exercise test, preceded by warming up and followed by cooling down. Per session, this load was increased, until the attained heart rate was equal to the heart rate at the anearobic threshold as estimated during the baseline test. Subsequent rowing or walking during 15 minutes was optional. Additionally, light resistance training was performed, consisting of 1 series of 25 repetitions of each of: flies, rowing, chest press, shoulder press, leg extension, leg curl, leg press and pull down. Resistance training intensity was adjusted in such a way that the patient experienced nearly-complete exhaustion of the involved muscle group after 25 repetitions.

Statistics

Data are expressed as mean ± standard deviation. Baseline characteristics were evaluated by using Mann-Whitney U test or chi-square tests with Yates correction. An unpaired Student's t-test was used to compare baseline values between the training and the control groups, and to test on changes in $\dot{V}O_{2\,peak}$, $\Delta\dot{V}O_2/\Delta W$, $\dot{V}E/\dot{V}CO_2$ slope, OUES and maximal workload (W_{max}). Changes in NYHA class within group T were evaluated with a Wilcoxon signed rank test. Linear regression analyses were performed to evaluate the relationship between $\Delta\dot{V}O_2/\Delta W$ and the baseline values of the other cardiopulmonary oxygen uptake variables ($\dot{V}O_{2\,peak}$, OUES and $\dot{V}E/\dot{V}CO_2$ slope). Linear

regression was also performed to asses the relationship between $\Delta\dot{V}O_2/\Delta w$ baseline values and $\Delta\dot{V}O_2/\Delta w$ changes.

RESULTS

Patient characteristics

Characteristics of the patients in group T (N=18) and group C (N=18) groups are summarized in *Table 1*. No significant differences were found between any of the characteristics of the patients in the T and C group. There were also no significant differences in baseline exercise testing variables (*Table 2*). Throughout the study, medication remained the same for all patients.

New York Heart Association classification

NYHA class improved after exercise training ($P<0.01$): 8 patients improved one NYHA class, while 8 patients remained in their NYHA class. NYHA class values after exercise training were missing for 2 patients.

Table 1. *Patient characteristics.*

	Exercise group	Control group	*P*-value
Sex	15M/3F	17M/1F	0.60
Age (years)	60 ± 11	63 ± 9	0.41
NYHA class I/II/III/IV	0/11/7/0	0/10/8/0	0.74
Etiology			0.18
Ischemic	8 (44%)	6 (34%)	
Non-ischemic	10 (56%)	13 (66%)	
BMI (kg/m²)	27.9 ± 5.9	28.1 ± 2.9	0.92
LVEF (%)	32 ± 7	33 ± 7	0.75
Medication			NS
ACE inhibitor/ AII blocker	14 (78%)	16 (89%)	
Diuretic	11 (61%)	12 (67%)	
Spironolactone	4 (22%)	3 (17%)	
Beta-blocker	13 (72%)	14 (78%)	
Amiodarone	2 (11%)	2 (11%)	

Legend to Table 1. BMI: body mass index (kg·m⁻²); F: female; M: male; LVEF: left ventricular ejection fraction; NS: not significant ($P>0.05$); NYHA: New York Heart Association functional class.

Table 2. *Changes in exercise testing variables.*

	Training Group		Control Group	
	Baseline	Remeasurement	Baseline	Remeasurement
$\dot{V}O_{2\,peak}$ (ml O_2/kg/min)	14.9 ± 4.8	18.3 ± 4.7*	16.6 ± 3.8	15.5 ± 4.5
$\dot{V}E/\dot{V}CO_2$slope	34.2 ± 9.4	30.9 ± 6.5*°	35.7 ± 5.8	36.2 ± 6.8
OUES [(mlO_2/min)/(L $\dot{V}E$/min)]	1558 ± 438	1845 ± 424*°	1786 ± 518	1768 ± 477
$Workload_{max}$ (Watt)	94.8 ± 31.4	110.9 ± 37.5*°	105.7 ± 27.4	101.8 ± 31.6
$\Delta\dot{V}O_2/\Delta w$ ((mlO_2/min)/Watt)	9.42 ± 1.27	9.41 ± 0.80	9.69 ± 1.06	9.57 ± 1.19

Legend to Table 2. OUES: oxygen uptake efficiency slope; $\Delta\dot{V}O_2/\Delta w$: oxygen uptake-work relation; $\dot{V}O_{2\,peak}$: peak oxygen uptake; $Workload_{max}$: maximal workload; *: baseline versus remeasurement $P<0.01$; °: change in training group versus change in control group $P<0.01$.

Exercise capacity

Exercise training improved $\dot{V}O_{2\,peak}$, OUES, w_{max} and $\dot{V}E/\dot{V}CO_2$ slope, but it did not improve $\Delta\dot{V}O_2/\Delta w$ ($P=0.99$, *Table 2*). However, 50% of group C and 33% of group T had relatively normal $\Delta\dot{V}O_2/\Delta w$ values ($\Delta\dot{V}O_2/\Delta w>10$ (ml/min)/Watt). We divided group T and group C in a population with $\Delta\dot{V}O_2/\Delta w>10$ (normal) and a population with $\Delta\dot{V}O_2/\Delta w<10$ (subnormal). Exercise training improved $\Delta\dot{V}O_2/\Delta w$ in the population with $\Delta\dot{V}O_2/\Delta w$ <10 (N=12) from 8.71± 0.90 to 9.14 ± 0.78 (ml/min)/Watt (*Table 3*). In this population all other exercise testing variables also improved (*Table 3*). Furthermore, baseline $\Delta\dot{V}O_2/\Delta w$ was related with the exercise-induced change in $\Delta\dot{V}O_2/\Delta w$, $r^2=0.60$ (*Figure 1*).

There was only a weak correlation in baseline values between $\Delta\dot{V}O_2/\Delta w$ and $\dot{V}O_{2\,peak}$ ($r^2=0.12$, $P=0.02$), and between $\Delta\dot{V}O_2/\Delta w$ and OUES ($r^2=0.15$, $P=0.01$, *Figure 1*). No correlation was found between $\Delta\dot{V}O_2/\Delta w$ and $\dot{V}E/\dot{V}CO_2$ slope ($r^2=0.02$, $P=0.41$, *Figure 1*). There was no significant difference between the $\Delta\dot{V}O_2/\Delta w$ baseline values of CHF patients with NYHA class II and of patients with NYHA class III (9.74 ± 0.93 versus 9.28 ± 1.41 (ml/min)/Watt, $P=0.25$).

Table 3. *Changes in exercise testing variables in the training group with subnormal* $\Delta\dot{V}O_2/\Delta w$ *($\Delta\dot{V}O_2/\Delta w<10$ ((ml/min)/Watt).*

N = 12	Baseline	Remeasurement
$\dot{V}O_{2\,peak}$ (ml O_2/kg/min)	14.4 ± 4.3	18.08 ± 4.2*
$\dot{V}E/\dot{V}CO_2$slope	36.1 ± 10.6	33.3 ± 6.6*
OUES [(mlO_2/min)/(L $\dot{V}E$/min)]	1448 ± 352	1707 ± 361*
$Workload_{max}$ (Watt)	91 ± 28	106 ± 26*
$\Delta\dot{V}O_2/\Delta w$ ((mlO_2/min)/Watt)	8.71 ± 0.90	9.14 ± 0.78+

Legend to Table 1. OUES: oxygen uptake efficiency slope; $\Delta\dot{V}O_2/\Delta w$: oxygen uptake-work relation; $\dot{V}O_{2\,peak}$: peak oxygen uptake; $Workload_{max}$: maximal workload; *: change in the training group versus change in the control group with subnormal $\Delta\dot{V}O_2/\Delta w$ $P<0.01$; +: change in the training group versus change in the control group with subnormal $\Delta\dot{V}O_2/\Delta w$ $P<0.04$.

DISCUSSION

Exercise training improved $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$, OUES and w_{max}. In 42% of our study population, $\Delta\dot{V}O_2/\Delta w$ baseline values were normal. In patients with subnormal $\Delta\dot{V}O_2/\Delta w$ baseline values, exercise training improved $\Delta\dot{V}O_2/\Delta w$. The amount of exercise-induced change in $\Delta\dot{V}O_2/\Delta w$ was related to baseline $\Delta\dot{V}O_2/\Delta w$.

To our knowledge, this is the first study demonstrating the effect of exercise training on the oxygen uptake-work relation in CHF. $\Delta\dot{V}O_2/\Delta w$ is often seen as an aspect of the $\dot{V}O_2$ kinetics as $\Delta\dot{V}O_2/\Delta w$ determines the amplitude of the oxygen response on exercise in a constant workload test[1,32]. It is, however, not identical to the $\dot{V}O_2$ time constants measured during a constant workload test[36]. Only one previous study has reported on the effect of exercise training on the $\dot{V}O_2$ time constants[36]. In contrast with our study, they found that exercise training improved $\dot{V}O_2$ kinetics in CHF irrespective of their baseline values. This discrepancy can be explained by the fact that $\Delta\dot{V}O_2/\Delta w$ measures another aspect of the $\dot{V}O_2$ kinetics than the $\dot{V}O_2$ time constants.

Subnormal $\Delta\dot{V}O_2/\Delta w$ in CHF can be attributed to components of both oxygen delivery and oxygen utilization systems[1]. Recently Kemps and colleagues[18], suggested that in CHF the delay in $\dot{V}O_2$ kinetics is primarily due to limitations in oxygen delivery systems. In healthy persons cardiac output time constants are larger than $\dot{V}O_2$ time constants, indicating that, during exercise onset, oxygen delivery to skeletal muscles is in excess of the metabolic demand. Kemps and colleagues[18] demonstrated that in CHF patients no clear difference between the $\dot{V}O_2$ and cardiac output time constants existed. This would imply that oxygen delivery is the limiting factor for $\dot{V}O_2$ kinetics, hence, limitation in oxygen delivery systems could also be the limiting factor of $\Delta\dot{V}O_2/\Delta w$ in CHF.

In line with these findings, Itoh and colleagues showed that by administration of the phosphodiesterase inhibitor Enoximone, which increases vasodilatation and myocardial inotropy in CHF patients, $\Delta\dot{V}O_2/\Delta w$ increased acutely[16]. Also, they found a close association between $\Delta\dot{V}O_2/\Delta w$ and the rise in norepinephrine concentrations during exercise[15]. They suggested an important influence of blood flow redistribution on $\Delta\dot{V}O_2/\Delta w$ (increased sympathoexcitation during exercise causes vasoconstriction that is overruled by metabolically induced vasodilatation in the working muscle, hereby causing blood flow redistribution at the sacrifice of other organs). Hence, work efficiency is increased, a mechanism that compensates for the limited oxygen supply in CHF patients.

Cardiac output is an important variable in oxygen delivery. CHF patients have an attenuated cardiac output response to exercise, which also can be seen as a major cause of a decreased $\Delta\dot{V}O_2/\Delta w$[19,31]. Unfortunately, our exercise testing protocol does not allow for differentiation between cardiac and peripheral training effects. Several studies showed that exercise training improves the cardiac output response to exercise[8,13,30]. Also, Roditis and colleagues showed that exercise training increases $\dot{V}O_2$ kinetics particularly in phase I (the exercise phase in which cardiac output increases considerably) and speculated that this might imply cardiac function improvement[27]. However, it is known that exercise training also reduces vasoconstriction, improves endothelial dysfunction, decreases tissue inflammation and improves intrinsic skeletal muscle properties[5,6,10–13,23,25,28]. Likely, training effects will also occur within these systems. Also, these systems all influence each other. E.g., an increased cardiac output response may improve pulmonary gas exchange. Further research has to reveal to which extent each of the codeterminants of $\Delta\dot{V}O_2/\Delta w$ affects the degree of response to exercise training.

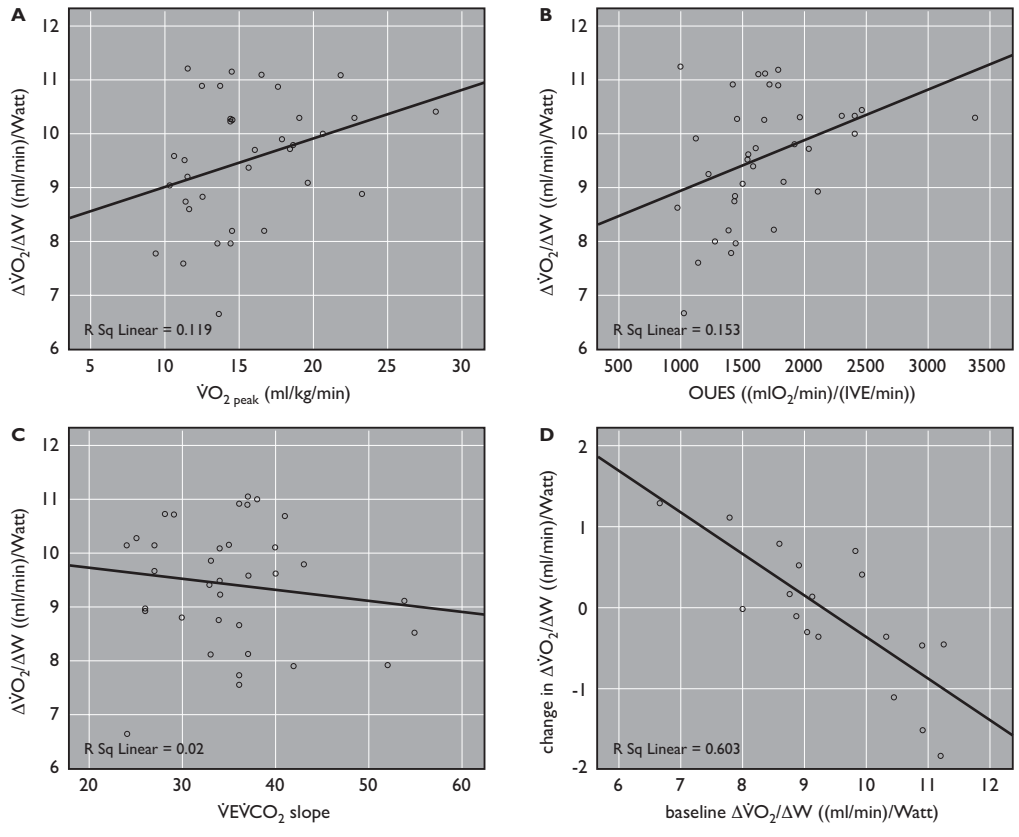


Figure 1. *Relation between* $\dot{V}O_{2\,peak}$, OUES, $\dot{V}E/\dot{V}CO_2$ *slope, change in* $\Delta\dot{V}O_2/\Delta w$ *after training and* $\Delta\dot{V}O_2/\Delta w$.
$\dot{V}O_{2\,peak}$*: peak oxygen uptake;* OUES*: oxygen uptake efficiency slope;* $\Delta\dot{V}O_2/\Delta w$*: oxygen uptake-work relation.*
Panel A: Relation between $\dot{V}O_{2\,peak}$ *and* $\Delta\dot{V}O_2/\Delta w$.
Panel B: Relation between $\dot{V}O_{2\,peak}$ *and* $\Delta\dot{V}O_2/\Delta w$.
Panel C: Relation between $\dot{V}E/\dot{V}CO_2$ *slope and* $\Delta\dot{V}O_2/\Delta w$.
Panel D: Relation between baseline $\Delta\dot{V}O_2/\Delta w$ *and change in* $\Delta\dot{V}O_2/\Delta w$ *after exercise training (P = 0.001).*

A limitation of the $\Delta\dot{V}O_2/\Delta w$ measure is, that it is not uniquely determined by aerobic metabolism during exercise; it is codetermined by external work efficiency. If external work efficiency in a subject is low and oxygen utilization and delivery systems are not limited, $\Delta\dot{V}O_2/\Delta w$ will be higher[34]. For instance if a person is performing an exercise test for the first time, he/she may be pulling the cycle handlebars which will lead to an increase in $\dot{V}O_2$ that is not becoming evident in the amount of external work performed at the pedals of the ergometer. Therefore, in subjects with normal or high $\Delta\dot{V}O_2/\Delta w$, $\Delta\dot{V}O_2/\Delta w$ may decrease a little bit with training because of improved external work efficiency (concentration of all work at the pedals of the ergometer. This may also have happened in our study participants: panel D in *Figure 1* indicates that, in patients with normal baseline $\Delta\dot{V}O_2/\Delta w$ values, $\Delta\dot{V}O_2/\Delta w$ decreases after exercise training. If the influence of an improved work efficiency is apparent in the group with normal $\Delta\dot{V}O_2/\Delta w$ values, one may assume that patients with subnormal $\Delta\dot{V}O_2/\Delta w$ baseline values also improved in work efficiency, therefore, the actual improvement in aerobic metabolism may even be higher than the measured increase in $\Delta\dot{V}O_2/\Delta w$.

As $\Delta\dot{V}O_2/\Delta w$ is likely not sensitive enough to asses changes in exercise capacity in mild CHF patients and as $\Delta\dot{V}O_2/\Delta w$ is influenced by external work efficiency, evaluation of the severity of the disease or the effectiveness of an exercise training program in CHF patients cannot be performed properly by only assessing $\Delta\dot{V}O_2/\Delta w$. However, as all exercise testing parameters reflect different aspects of the

Normal $\Delta\dot{V}O_2/\Delta w$ values are around 10 (ml/min)/Watt [34,35]. Different from the other exercise testing variables, $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$, w_{max}, and OUES, 42% of our study population had normal baseline $\Delta\dot{V}O_2/\Delta w$ values. Cohen-Solal and colleagues[29] reported that $\Delta\dot{V}O_2/\Delta w$ values were significantly reduced in severely impaired ($\dot{V}O_{2\,peak}$ <16 ml/kg/min) CHF patients[29]. According to this definition, greater part of our population, 61%, was severely impaired. However, 35% of these patients had a baseline $\Delta\dot{V}O_2/\Delta w$>10 (ml/min)/Watt. Also there was no significant difference in $\Delta\dot{V}O_2/\Delta w$ in patients with NYHA II and NYHA III classification, and there existed only a weak correlation in baseline values between $\Delta\dot{V}O_2/\Delta w$ and $\dot{V}O_{2\,peak}$ and OUES (*Figure 1*). Therefore, different from the study by Cohen-Solal and colleagues[29], we found no strong association between the severity of CHF and $\Delta\dot{V}O_2/\Delta w$. However, our study population was relatively small (N=36). Also, the used exercise testing protocol influences on the $\Delta\dot{V}O_2/\Delta w$. Hansen and colleagues[14] showed that $\Delta\dot{V}O_2/\Delta w$ changed when different slopes of the work rate increment were used (the slower the increment in work rate, the higher $\Delta\dot{V}O_2/\Delta w$). However, the slope of the work rate increment in our exercise testing protocol was identical to that of the one used by Cohen-Solal and colleagues[29], there was only a difference in initial workload (20 watts in the study of Cohen-Solal and colleagues versus 5 watts in our study).

cardiopulmonary system during exercise, we think it is still of importance to assess $\Delta\dot{v}o_2/\Delta w$ in combination with other cardiopulmonary exercise training variables like $\dot{v}o_{2\,peak}$, $\dot{v}E/\dot{v}CO_2$ slope and OUES. We are of opinion that assessing all exercise testing variables together for each individual will make it possible to establish a more reliable representation of the patient's individual capabilities and drawbacks. Also, exercise testing variables have all individually important prognostic value[7,20] and, combining these variables might lead to a powerful prognostic tool. Further research to investigate this, and to investigate if exercise-induced $\Delta\dot{v}o_2/\Delta w$ improvements are associated with improved prognosis, is needed.

Limitations

Although the time interval between the initial and second symptom-limited exercise tests is probably not of utmost importance, it is a limitation that there is a discrepancy in time between the performance of the first and second symptom limited exercise test between the C and T groups. This difference was a result caused by our principle that the start of the rehabilitation program of the control patients should not be delayed by our study.

Also, as mentioned in the discussion, it is a limitation that $\Delta\dot{v}o_2/\Delta w$ is not uniquely determined by the aerobic metabolism, as it is also codetermined by the external work efficiency.

CONCLUSIONS

Exercise training improved $\dot{v}o_2$ peak, $\dot{v}E/\dot{v}CO_2$, w_{max}, and OUES. In half of our population $\Delta\dot{v}o_2/\Delta w$ baseline values were normal. In patients with decreased $\Delta\dot{v}o_2/\Delta w$ exercise training improved $\Delta\dot{v}o_2/\Delta w$. Follow-up studies are needed to demonstrate if exercise-induced $\Delta\dot{v}o_2/\Delta w$ improvements are associated with improved prognosis.

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BIVENTRICULAR PACING IN CHRONIC HEART FAILURE ACUTELY FACILITATES THE ARTERIAL BAROREFLEX

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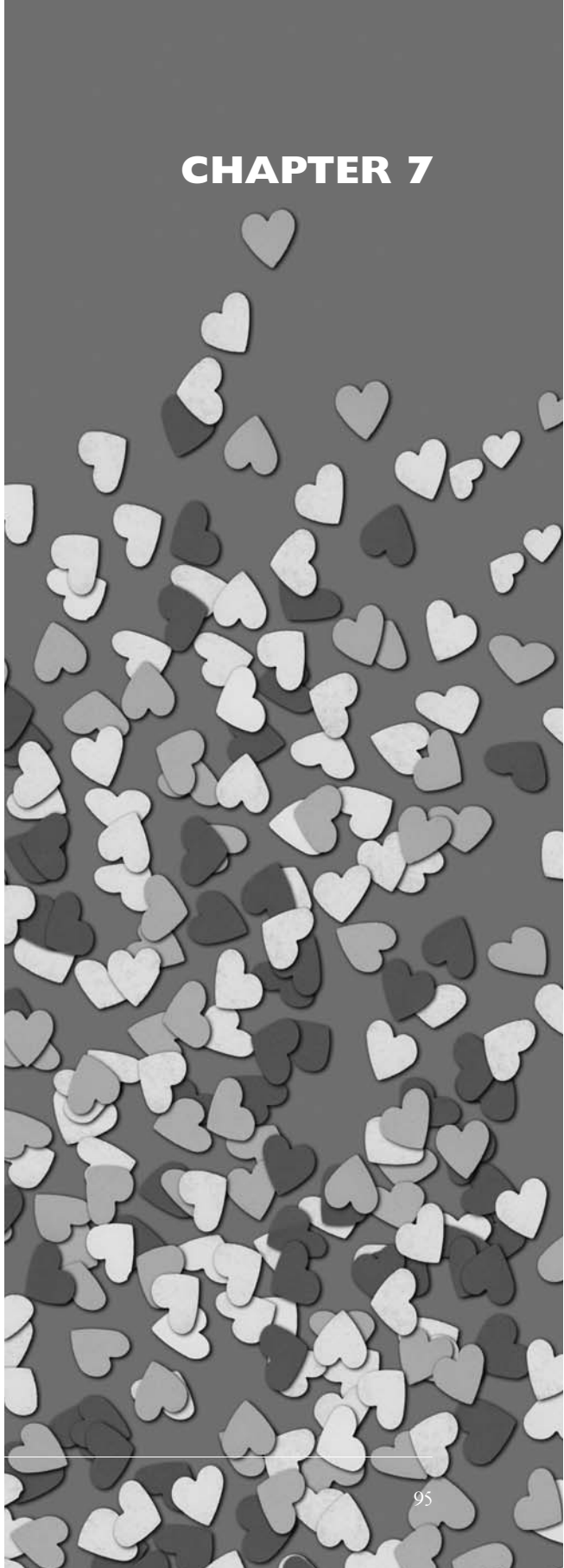

ABSTRACT

Background. Metabolic and mechanical stress in the failing heart activates the cardiac sympathetic afferent reflex (CSAR). It has been demonstrated that cardiac resynchronization therapy (CRT) acutely reduces muscle sympathetic nerve activity in clinical responders. Mechanistically, this beneficial effect might be explained by acute deactivation of the CSAR. In addition to sympathoexcitation, CSAR inhibits the arterial baroreflex at the level of the nucleus tractus solitarii. Hence, in responders, CRT is likely to remove/reduce this inhibition. Therefore, we hypothesized that CRT acutely facilitates the arterial baroreflex.

Methods and Results. One day after implantation of a CRT device in 32 patients with chronic heart failure (left ventricular ejection fraction (LVEF), 27 ± 6%) we measured noninvasive baroreflex sensitivity (BRS) and heart rate variability (HRV) in two conditions: CRT device switched on and switched off (on/off order randomized). BRS changes were correlated with the difference in unpaced/paced LVEF, a measure of acute mechanical response to CRT. CRT increased BRS by 28% from 2.96 to 3.79 ms/mmHg ($P<0.02$) and increased HRV (standard deviation of the intervals between normal beats) from 18.5 to 24.0 ms ($P<0.01$). The CRT induced relative change in BRS correlated with the change in LVEF ($r=0.44$, $P<0.01$).

Conclusion. CRT acutely increases BRS and HRV. This favourable response of the autonomic nervous system might be caused by CRT-induced CSAR deactivation. Follow-up studies should verify the mechanism of the acute response and the possible predictive value of an acute positive BRS response.

INTRODUCTION

Chronic heart failure (CHF) is characterized by permanent neurohumoral activation, i.e., elevated sympathetic tone, depressed parasympathetic tone and activation of the renin-angiotensin-aldosteron system. This neurohumoral activation is accompanied by an increased peripheral chemoreflex and a decreased arterial baroreflex. Baroreflex sensitivity (BRS) has independent prognostic value in CHF[20]

Several mechanisms play a role in the blunting of the arterial baroreflex in CHF, e.g. an increased sympathetic outflow, an increase in circulating and central angiotensin II, an increased chemoreflex and an increased cardiac sympathetic afferent reflex. (CSAR)[13,19]. CSAR, a reflex that is not excited in the normal heart at rest, is activated by mechanical stretch and by metabolites like potassium, hydrogen ion, adenosine, bradykinin and prostaglandins, which are elevated during myocardial ischemia and with cardiac stretch[25,34]. In CHF, CSAR is not only enhanced because of an increase in discharge intensity at the receptor level but also because of an increase in central reflex gain[18,38].

Cardiac resynchronization therapy (CRT), a relatively new therapy in CHF, is known to acutely decrease left ventricular (LV) dyssynchrony, to lower left LV filling pressure and to increase myocardial efficiency[32,37]. Besides these acute effects on cardiac functioning, CRT also induces acute effects in autonomic functioning. Najem et al.[21] showed that muscle sympathetic nerve activity (MSNA) acutely increased in responders of CRT when biventricular pacing was switched off. A plausible and clinically relevant explanation for this observation 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. Since CSAR afferent firing is known to decrease arterial baroreflex sensitivity (BRS)[13,38], CRT-induced CSAR deactivation should be accompanied by a BRS increase. Therefore, we hypothesized that biventricular pacing acutely facilitates the arterial baroreflex.

Although a CRT-induced BRS increase is not sufficient to prove that CRT deactivates CSAR, it is a necessary condition. Hence, in addition to a possible improved prognosis, the significance of finding a CRT-induced BRS increase is that it comports suggestive evidence for CSAR deactivation as one possible working mechanism of CRT, underlining the need for further experimental verification.

METHODS

Patients

The protocol was approved by the local Medical Ethics Committee. Thirty-two consecutive CHF patients eligible for CRT implantation were included in this study. Patients with atrial fibrillation, atrioventricular conduction defects or frequent supraventricular or vertricular ectopy were not included, as noninvasive baroreflex sensitivity measurement requires sinus rhythm.

Protocol

Baseline echocardiography was performed on the day of implantation preceding the implantation procedure. One day after implantation of a CRT device, echocardiography was repeated and a BRS and heart rate variability (HRV) evaluation was performed. BRS and HRV were measured in each patient in two conditions: CRT device switched on and switched off (on/off order randomized). After the first BRS and HRV evaluation, CRT modality was changed conform the randomization protocol. After this change in CRT modality 10 minutes of rest followed prior to the second BRS and HRV evaluation.

Instrumentation

During baroreflex and HRV evaluation the patients were in the supine position. To prevent respiratory discomfort, the upper part of the bed was inclined in accordance with the individual's sleeping habits. The fingercuff of a continuous noninvasive arterial blood pressure measurement device (Finometer, Finapres Medical Systems, Amsterdam, NL) was attached around the second phalanx of the left middle finger. The armcuff of an automatic sphygmometer (Accutorr 3, Datascope Corp., Montvale, NJ, USA) was attached around the right upper arm. A standard 12-lead ECG was derived. Two electrodes were applied to the lateral sides of the lower part of the thorax to monitor respiration (impedance method). Blood pressure, respiration and ECG were recorded with an ST-surveyor monitoring system (Mortara Rangoni Europe, Casalechio di Reno, BO, Italy) with a 500 Hz sampling rate.

Measurements

First, blood pressure and heart rate (Accutorr, average of 5 subsequent readings) were measured after a 15-minute resting period. These measurements were used to establish a reliable systolic blood pressure (SBP) measurement with the noninvasive arterial blood pressure measurement device. Then, after the patient had been lying for 30 minutes, the ECG, the noninvasive continuous arterial blood pressure signal and the respiration signal were recorded during 10 minutes for later BRS and HRV calculation. During this period, patients performed 0.25-Hz metronome respiration (preventing the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency band (0.04-0.15 Hz), in which we compute BRS)[12]. After switching the CRT device on or off and an additional 10 minutes of rest, this measurement was repeated.

BRS and HRV calculation

To characterize arterial baroreflex function we computed BRS, the reflex-induced increase/decrease of the interval between heart

beats, in milliseconds, per unit rise/fall of SBP. First, the arrhythmia free and stationary periods longer than 60 seconds in the metronome respiration episode were selected (stationary sinus rhythm and blood pressure are prerequisites for a reliable BRS value). Compliance to the metronome respiration protocol was visually verified in the respiration signal. Then, BRS was computed in each of the selected episodes. The BRS algorithm computes the magnitude of the transfer function between the systolic blood pressure variability (baroreflex input) and the interbeat interval (IBI) variability (output), averaged over the 0.04-0.15 Hz band. Additionally, it calculates 95% two-sided BRS confidence intervals[33]. Finally, the overall BRS was composed from all data segments by the best linear unbiased estimator (BLUE) method[36]. Mean SBP and mean IBI were computed from the selected episodes. HRV was expressed as the standard deviation of the intervals between normal beats (SDNN).

Echocardiography

Echocardiographic images were obtained in the left lateral decubitus position using a commercially available system (Vivid 7, General Electric – Vingmed, Milwaukee, WI, USA). A minimum of 2 consecutive heart beats was recorded from each view and the images were digitally stored for off-line analysis (EchoPac, General Electric Vingmed Ultrasound, Milwaukee, USA). LV end-systolic (LVESV) and end-diastolic (LVEDV) volumes and LV ejection fraction (LVEF) were calculated from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule[30].

Lv dyssynchrony was assessed by tissue Doppler imaging on the apical 2- and 4-chamber view and calculated as the maximum time delay between the peak systolic velocities of 4 opposing basal walls[4].

The sample volume was placed between the tips of the mitral leaflets to assess Doppler pulsed-wave mitral inflow. The mitral inflow peak early velocity (E) to mitral annular peak early velocity (E'), or E/E' ratio was assessed by dividing E by E' at the basal septal segment[22].

Statistics

Results are presented as mean ± SD. A paired Student's t-test was used to evaluate the changes in BRS, HRV, LV dyssynchrony, LVEF, LVEDV, LVESV, E/E' ratio, SBP and IBI between the different CRT modes. Linear regression analyses was performed to evaluate the relationship between CRT-associated LVEF change and BRS change.

RESULTS

Study group

Baseline characteristics of the study group are listed in *Table 1*. A total of 32 patients were included. All CRT devices were successfully implanted (Contak Renewal (n=16), Guidant, MN, USA; InSync Sentry (n= 14), Medtronic Inc., MN, USA; Concerto (n= 1), Medtronic Inc., MN, USA; Lumax (n= 1), Biotronic, MI, USA). The atrioventricular delay (AV-delay) was optimized by two-dimensional echocardiography so that it provided the longest filling time for completion of the end-diastolic filling flow before LV contraction, AV-delay was set at 120 ± 10 ms. No adjustments were made to the interventricular pacing delay (V-V interval; set at 0 ms).

Table 1. *Patient characteristics before pacemaker implantation.*

Sex		26M/6F
Age (years)		66 ± 9
NYHA class I/II/III/IV		2/13/15/2
Etiology		
	Ischemic	17 (47%)
	Non-ischemic	15 (53%)
QRS duration (ms)		154 ± 30
LVEF (%)		27 ± 6
LVEDV (ml)		227 ± 79
LVESV (ml)		168 ± 63
LV dyssynchrony (ms)		62 ± 43
Medication		
	ACE inhibitor/AII blocker	30 (94%)
	Diuretic	22 (69%)
	Spironolactone	17 (53%)
	Beta-blocker	27 (84%)
	Amiodarone	6 (19%)

Legend to Table 1. LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association.

BRS, HRV, SBP and IBI

BRS was significantly larger with biventricular pacing than without: 3.79 ± 4.04 ms/mmHg and 2.96 ± 3.19 ms/mmHg, respectively (average individual change 28%, $P<0.05$). SDNN was also larger with biventricular pacing than without: 24.0 ± 14.3 ms and 18.5 ± 9.5 ms, respectively (average individual change 30%, $P<0.05$). SBP and IBI did not change significantly (*Table 2*).

LV dyssynchrony, LVEF, LVEDV, LVESV and E/E' ratio

In one person it was not possible to asses LVEF due to poor quality of the acoustic window. With biventricular pacing, LV dyssynchrony, LVEDV, LVESV and E/E' ratio decreased from 62 ± 43 ms to 35 ± 38 ms ($P<0.001$), from 227 ± 79 ml to 216 ± 77 ml ($P<0.001$), from 168 ± 63 ml to150 ± 63 ml ($P<0.001$) and from 19.0 ± 9.3 to 15.6 ± 8.1 ($P<0.005$), respectively. LVEF increased from 27 ± 6% to 32 ± 7% ($P<0.001$) (*Table 2*).

Correlations between changes in BRS and in LVEF.

The relative change in BRS correlated with the relative change in LVEF (r= 0.44, $P<0.01$) (*Figure 1*).

Ischemic versus nonischemic etiology

There were 15 patients with nonischemic etiology and 17 patients with ischemic etiology. In both groups BRS tended to be larger with biventricular pacing than without: in the nonischemic group BRS increased by 30% from 3.15 ± 4.5 ms/mmHg to 4.10 ± 5.5 ms/mmHg ($P=0.08$) and in the ischemic group BRS increased by 28% from 2.79 ± 1.4 ms/mmHg to 3.51 ± 2.37.1 ms/mmHg ($P=0.10$). No significant difference in increase in BRS was found between the two groups ($P=0.85$).

DISCUSSION AND CONCLUSION

Our data demonstrate that CRT acutely increases BRS and HRV irrespective of etiology; the relative change in BRS correlates with the change in LVEF.

Table 2. *Outcome variables with and without biventricular pacing.*

	CRT device off	CRT device on	P
BRS (ms/mmHg)	2.96 ± 3.19	3.79 ± 4.04	< 0.02
SDNN (ms)	18.5 ± 9.5	24.0 ± 14.3	< 0.01
SBP (mmHg)	109.6 ± 19.2	110.5 ± 19.1	0.54
IBI (ms)	857 ± 165	864 ± 164	0.11
LVdyssynchrony (ms)	62 ± 43	35 ± 38	< 0.001
LVEF (%)	27 ± 6	32 ± 7	< 0.001
LVEDV (ml)	227 ± 79	216 ± 77	< 0.001
LVESV (ml)	168 ± 63	150 ± 63	< 0.001

Legend to Table 2. BRS: baroreflex sensitivity; CRT: cardiac resynchronization therapy; IBI: inter beat interval; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; SBP: systolic blood pressure; SDNN: standard deviation of the intervals between normal heart beats.

Lv dyssynchrony is associated with a decline in systolic performance, an increase in end-systolic volume and wall stress, a delayed relaxation and a decline in myocardial efficiency[14,26]. Lv dyssynchrony is probably one of the factors causing CSAR activation, as CSAR is activated under influence of metabolic and mechanical stress in the failing heart[38]. Optimization of the mechanical activation pattern of the left ventricle is the primary working mechanism of CRT[17]. CRT induces early excitation of the region which is otherwise late activated due to delayed intrinsic conduction. In concordance with other studies[8] we found that CRT acutely decreased LV dyssynchrony as well LV filling pressures, expressed as E/E' ratio (*Table 2*). Previous studies have also shown that CRT acutely lowers LV filling pressures[37] and enhances myocardial efficiency[32]. Moreover, Nelson et al.[23] found that CRT enhanced systolic function with modestly diminished energy cost, which is probably explained by lowering of lateral wall stress. Hence resynchronization might well reduce CSAR activation.

A schematic representation of the CSAR pathway is outlined in *Figure 2*. CSAR afferents project on the rostroventral lateral medulla (RVLM) and on the nucleus tractus solitarii (NTS). CSAR afferents activate sympathetic efferents at the level of the RLVM. At the level of the NTS, CSAR afferents activate interneurons[28,39]. These interneurons release the neuromodulator gamma-aminobutyric acid (GABA) that inhibits the barosensitive NTS neurons[39]. Thus, a decrease in CSAR afferent firing will lead to a stronger baroreflex. Several studies in normal animals and in animals with heart failure have shown that electrical or mechanical stimulation of CSAR decreases BRS[13,38]. We found that BRS was larger with the CRT device switched on. Logically, the CRT induced increase in BRS as well as less excitation of the sympathetic efferents in the RVLM will contribute to a decreased sympathetic outflow, which was found by Najem et al.[21], who showed that stopping of CRT instantly increased MSNA.

Other factors than a decrease in CSAR afferent firing might also explain the improvement of BRS with biventricular pacing. In addition to cardiac sympathetic afferents, the NTS also receives projections of cardiac vagal afferents[5]. In heart failure, vagal mechanoreceptors are desensitized, possibly caused by continuous stretching of the receptors due to a sustained increase in left ventricular end-diastolic pressure (LVEDP)[7]. Like others[37],we found that CRT acutely decreased LVEDP (expressed as E/E' ratio; see *Table 2*). Hence, in addition to reducing CSAR afferent firing, CRT may positively influence vagal afferent mechanoreceptor functioning, by decreasing LVEDP. It is known that, at the NTS, cardiac vagal afferents interact occlusively with cardiac sympathetic afferents[34]. Hence, a weakened input at the NTS due to the CRT-mediated decrease in sympathetic afferent firing may have been further weakened by simultaneously occurring increased vagal afferent firing. It is difficult to draw conclusions about the likeliness of such an extra contribution to a BRS increase by CRT induced changes in vagal afferent activity. Paradoxically in healthy animals, stimulation of cardiac vagal mechanoreceptors results in an attenuated BRS[40] and no research has been conducted to establish the effect of cardiac vagal afferent stimulation on BRS in CHF.

CRT also acutely increases the maximal rate of LV pressure change (dP/dt_{max})[3]. An increase in dP/dt_{max} may cause more intense firing of the arterial baroreceptors which could increase BRS[10]. However, Eckberg[10] showed that variations of dP/dt_{max} within 550 to 3300 mmHg/sec did not influence BRS. As CHF patients have dP/dt_{max} values within this range[31], it is unlikely that the CRT induced increase in dP/dt_{max} will have influenced BRS.

Changes in SBP might also explain BRS improvement due to biventricular pacing since a change in SBP influences the logistic curve of

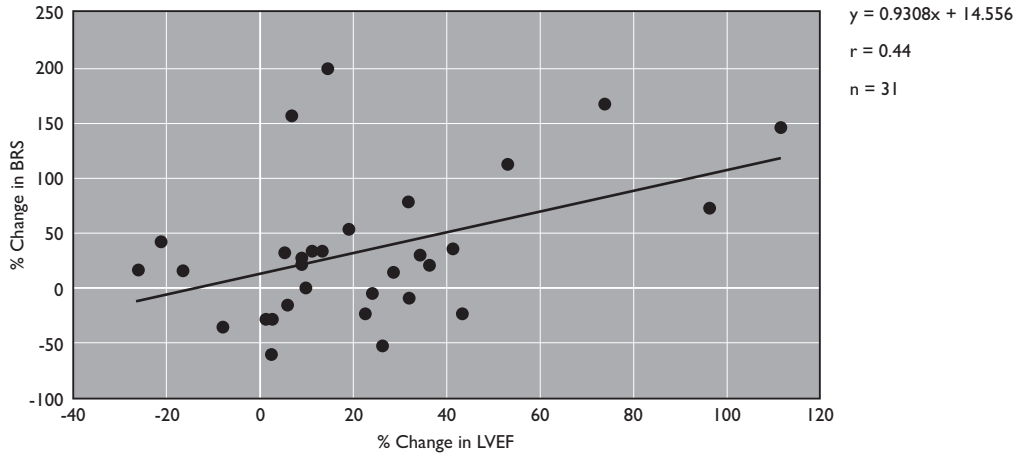

Figure 1. *Correlation between % change in* BRS *and* LVEF *(*CRT *switched off versus* CRT *switched on).* BRS*: baroreflex sensitivity;* CRT*: cardiac resynchronization therapy;* LVEF*: left ventricular ejection fraction.*

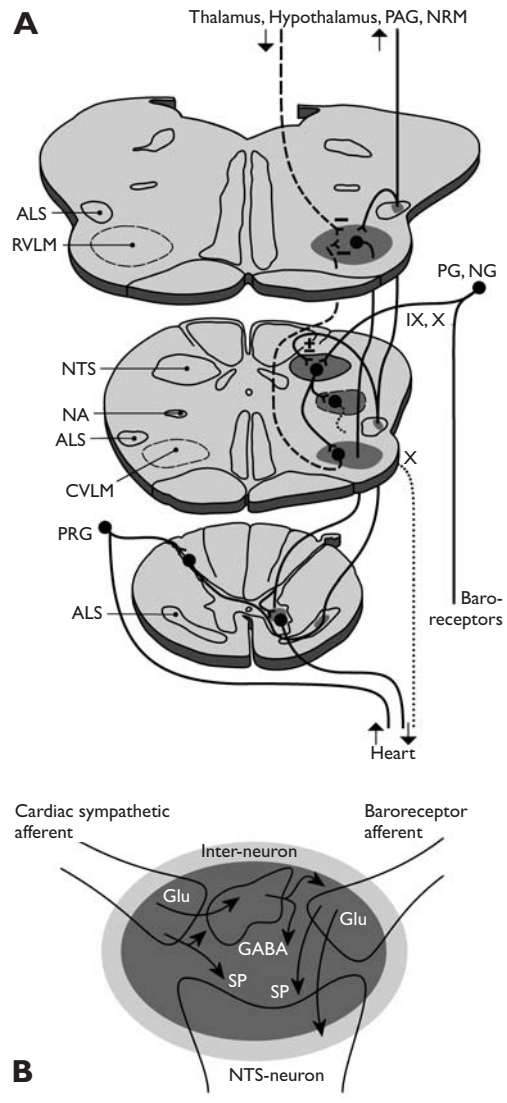

Figure 2. *Neural pathways involved in sympathoexcitation and baroreflex inhibition by cardiac sympathetic afferents.*
Panel A: sacral and thoracic spinal, and caudal and rostral medullar sections;
panel B: NTS *details (based on[28]).* ALS *= anterolateral (spinothalamic) system;* CVLM *= caudal ventrolateral 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.*

the BRS[15]. Blanc et al. showed with an invasive arterial blood pressure measurement at the level of the heart that CRT may acutely increase blood pressure[6]. We, however, did not find such an increase in SBP with CRT. This discrepancy might be caused by the different SBP measurement methods, since we did not measure SBP invasively but rather using a noninvasive device that measures arterial blood pressure more distally (at the finger). Whatever the cause of the difference in the observations by Blanc et al.[6] or the current study, our data do not support a possible influence of SBP on the logistic function curve of the BRS[15]. This leaves us with the plausible explanation of the observed CRT-induced BRS increase, *i.e.*, facilitation of the baroreflex due to CRT-induced CSAR deactivation. However, as recording of CSAR afferent activity is currently not possible in humans in vivo, new animal studies are needed to determine whether the CRT-induced BRS increase is indeed caused by CSAR deactivitation.

Seminal to our study was the publication by Sarzi et al.[29], who described in a case report that BRS normalized after 3 months of CRT. This finding is of high importance, therefore we tested this hypothesis on group level. Obviously, this case report could also not separate between the direct and indirect effect of CRT, *i.e.*, the direct effect of CRT in terms of a pacing-related reduction in CSAR afferent nerve traffic as described above, or the indirect effect of a BRS increase that might be due to on the long term remodelling and associated increase in dP/dt[31], and to the training effect of enhanced physical activity[27] that is to be expected in a patient in whom cardiac function is improved. In our current study, we noted that CRT acutely increased BRS; this proves the existence of a direct effect of CRT 1 day after implantation. It is however, not known wether this acute increase in BRS will be followed by a further gradual increase over time, and what could be the possible mechanism underlying such a further gradual increase. These issues demand clarification as lowered BRS in CHF parallels deterioration of clinical and hemodynamic status and is significantly associated with poor survival[20].

Also HRV has a strong prognostic value in CHF[24]. We used SDNN as a measure of HRV because SDNN is one of the most commonly computed HRV parameters. Furthermore, SDNN has the advantage that is not sensitive to algorithmic variants as seen in spectral HRV analysis[1], and can also be determined in short recordings like the standard diagnostic 12-lead ECG[9]. Several studies have already shown that CRT increases HRV[2,11], but to our knowledge, this is the first study to show that HRV increases acutely after initiation of biventricular pacing. The average individual increase in HRV (30%) was in line with the increase in BRS (28%). This is according to expectation: an increase in BRS will result in an increase in HRV because greater part of HRV is caused by baroreflex mediated vagal and sympathetic transmission of blood pressure variability to the sinus node[35].

When placed in a wider time perspective, the on-off experiments in our study could have been done earlier (immediately after CRT implantation) or later (e.g., 3 or 6 months after CRT implantation). The earlier these measurements, the purer the on-off BRS difference reflects the acute effect of CRT institution. When measured later, the on-off BRS difference gives rather an impression of the acute effect of CRT withdrawal than of CRT institution, as therapeutic effects like inverse remodelling might have occurred. Therefore, we have chosen for the most early evaluation moment possible; earlier than 1 day after implantation would have confounded the measurements with the implantation procedure-related effects of stress and anaesthetics on BRS.

Our protocol was designed to study differences in BRS and thereby to probe the mechanism by which CRT might exert its beneficial influence. We interpret an acute BRS increase with CRT as suggestive evidence for inactivation of CSAR by CRT. Basically, the magnitude of the BRS response is here less important, as long as the BRS increase with CRT remains demonstrable. Theoretically, we could have measured a larger contrast between the CRT-on and CRT-off BRS if we had chosen for longer periods during which CRT was on or off. In the current protocol this period was 10 minutes. By inclusion of a BRS measurement before implantation of the CRT device, we could have verified wether BRS, after switching of the pacemaker, returned to preimplantation values. This, and related questions, address another interesting research topic, namely what influence CRT has on BRS in terms of a prognostic factor[16] and if the acute effect as we measured it has predictive value for the long-term effect. This issue was not addressed by our protocol, however.

Brs changes correlated significantly, but weakly (r=0.44), with the changes in LVEF, which we used as a measure of acute mechanical response to CRT. As the acute change in BRS correlated with acute mechanical response to CRT, we would also expect a correlation between acute BRS and late mechanical response. Long-term follow-up studies are needed to verify if acute BRS increase facilitated by CRT predicts clinical outcome.

CONCLUSIONS

Crt acutely facilitates the baroreflex. Further studies should verify wether this positive effect is caused by CRT-induced CSAR deactivation. Also, the predictive value of the limited acute BRS increase as we found for a possible further BRS increase with time[16] and for a positive clinical response to CRT should be investigated.

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CHAPTER 8

BIVENTRICULAR PACING-INDUCED ACUTE RESPONSE IN BAROREFLEX SENSITIVITY HAS PREDICTIVE VALUE FOR MID-TERM RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

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ABSTRACT

Background. In a previous study we demonstrated that institution of biventricular pacing in chronic heart failure (CHF) acutely facilitates the arterial baroreflex. The arterial baroreflex has important prognostic value in CHF. We hypothesized that the acute response in baroreflex sensitivity (BRS) after institution of cardiac resynchronization therapy (CRT) has predictive value for mid-term response.

Methods. One day after implantation of a CRT device in 33 CHF patients (27 male / 6 female, age 66.5 ± 9.5 years, left ventricular ejection fraction 28 ± 7%) we measured noninvasive BRS and heart rate variability (HRV) in two conditions: CRT device switched-on and switched-off (on/off order randomized). Echocardiography was performed prior to implantation (baseline) and 6 months after implantation (follow-up). CRT responders were defined as patients in whom left ventricular end systolic volume (LVESV) at follow-up had decreased by ≥ 15%.

Results. Responders (69.7%) and non-responders (30.3%) had similar baseline characteristics. In responders, CRT increased BRS by 30% (P=0.03); this differed significantly (P=0.02) from the average BRS change (-2%) in the non-responders. Also, CRT increased HRV by 30% in responders (P=0.02), but there was no significant difference found compared to the increase in HRV (8%) in the non-responders. Receiver-operating characteristic (ROC) curve analysis revealed that the percetage BRS increase had predictive value for the discrimination of responders and non-responders (area-under-the-curve 0.69; 95% confidence interval 0.51-0.87; maximal accuracy 0.70).

Conclusions. Our study demonstrates that a CRT-induced acute BRS increase has predictive value for the anatomical response to CRT. This finding suggests that the autonomic nervous system is actively involved in CRT-related reverse remodelling.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a relatively new and effective therapy in drug-refractory chronic heart failure (CHF). Studies have demonstrated that CRT decreases mortality and symptoms, and improves quality of life and New York Heart Association (NYHA) class[1,9]. Unfortunately, not all CHF patients experience positive effects of biventricular pacing: about 30% of the patients with an implanted device do not respond to CRT[3,4,22]. Therefore, several studies have been and are being conducted to identify measures that predict a positive response to CRT.

Permanent neurohumoral activation, *i.e.*, elevated sympathetic tone, depressed parasympathetic tone and activation of the renin-angiotensin-aldosterone system, is a hallmark of CHF. Simultaneously with neurohumoral activation, CHF patients have an increased peripheral chemoreflex and a decreased arterial baroreflex. Most therapies in CHF aim to diminish the detrimental influences of this neurohumoral activation and autonomic derangement by pharmacological interruption of the formation of the involved neurohormones or by blocking their effect at the receptor level.

CRT seems to have an acute beneficial effect on the permanent neurohumoral activation and autonomic derangement in CHF. Hamdan et al. found that biventricular pacing acutely reduced muscle sympathetic nerve activity (MSNA) when compared to right ventricular pacing[13]. Also, Najem et al.[17] showed that MSNA acutely increased in responders of CRT when biventricular pacing was switched off, this was not the case in non-responders of CRT. Furthermore, as we recently demonstrated, the arterial baroreflex sensitivity (BRS) is acutely improved with CRT[11]. It is, however, currently unknown if such acute CRT-induced autonomic responses are associated with clinical outcome.

As BRS is an important independent prognostic parameter in CHF[16], we hypothesized that patients showing an acute CRT-induced BRS increase one day after implantation, will respond positively to CRT.

METHODS

Patients

The protocol was approved by the local Medical Ethics Committee. Consecutive CHF patients eligible for CRT implantation were included in this study. Patients with atrial fibrillation, AV-conduction defects or frequent supraventricular or ventricular ectopy were not included, as sinus rhythm is a prerequisite for reliable noninvasive BRS measurement.

Protocol

One day after implantation, a BRS and heart rate variability (HRV) evaluation was performed. BRS and HRV were measured in each patient in two conditions: CRT device switched on and switched off (on/off order randomized). After the first BRS and HRV evaluation the CRT modality was changed according to the randomization protocol. After changing CRT modality, 10 minutes of rest followed, hereafter, the second BRS and HRV evaluation took place. Echocardiography was performed prior to the implantation procedure on the day of implantation, and was repeated 6 months after implantation.

BRS and HRV evaluation

Instrumentation

During BRS and HRV evaluation the patients were in the supine position. The upper part of the bed was inclined in accordance with the individual sleeping habit, to prevent respiratory discomfort. Around the second phalanx of the left middle finger, the fingercuff of a continuous noninvasive arterial blood pressure measurement device (Finometer, Finapres Medical Systems, Amsterdam, NL) was attached. Around the right upper arm, the armcuff of an automatic sphygmometer (Accutorr 3, Datascope Corp., Montvale, NJ, USA) was attached. A standard 12-lead ECG was continuously recorded during the measurement procedure. To the lateral sides of the lower part of the thorax, two electrodes were applied in order to monitor respiration (impedance method). Blood pressure, ECG and respiration were recorded with an ST-surveyor monitoring system (Mortara Rangoni Europe, Casalechio di Reno, BO, Italy) with a 500 Hz sampling rate.

Measurements

First, blood pressure and heart rate (Accutorr, average of 5 subsequent readings) were measured after a 15-minute resting period. These blood pressure measurements were used as a gold standard and were compared with the noninvasive arterial blood pressure measurement device. In this way, a reliable noninvasive arterial blood pressure measurement could be established. When the patient had been lying for 30 minutes, the noninvasive continuous arterial blood pressure signal, the ECG and the respiration signal were recorded during 10 minutes for later HRV and BRS calculation. During this period, patients performed 0.25 Hz metronome respiration (preventing the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency band (0.04-0.15 Hz), in which we compute BRS)[10]. This measurement was repeated, after switching the CRT device on or off and an additional 10 minutes of rest.

Analysis

To characterize arterial baroreflex function we computed BRS, the reflex-induced increase/decrease of the interval between heart beats, in milliseconds, per unit rise/fall of systolic blood pressure. All signals were blindly analyzed. First, the arrhythmia free and stationary periods longer than 60 seconds in the metronome respiration episode were selected (stationary sinus rhythm and blood pressure are prerequisites for a reliable BRS value). Compliance to the metronome respiration protocol was visually verified in the respi-

ration signal. Then, BRS was computed in each of the selected episodes. The BRS algorithm computes the magnitude of the transfer function between the systolic blood pressure variability (baroreflex input) and the interbeat interval variability (output), averaged over the 0.04–0.15 Hz band. Additionally, it calculates 95% two-sided BRS confidence intervals (CI)[27]. Finally, the overall BRS was composed from all data segments by the best linear unbiased estimator (BLUE) method[30]. Mean systolic blood pressure (SBP) and mean inter beat interval (IBI) were computed by taking the average of all SBP and IBI values from the selected episodes. HRV was also computed from the selected episodes and expressed as the standard deviation of the intervals between normal beats (SDNN).

Echocardiography

Echocardiographic images were obtained in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric – Vingmed, Milwaukee, WI, USA). A minimum of two consecutive heart beats was recorded from each view and the images were digitally stored for off-line analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Left ventricular (LV) end-systolic and end-diastolic volumes and LV ejection fraction (LVEF) were calculated from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule[23].

Lv dyssynchrony was assessed by tissue Doppler imaging on the apical 2- and 4-chamber views and calculated as the maximum time delay between the peak systolic velocities of 4 basal walls[2]. The sample volume was placed between the tips of the mitral leaflets to assess Doppler pulsed-wave mitral inflow.

Clinical evaluation

Prior to implantation and after 6 months of CRT, clinical evaluation took place consisting of NYHA class assessment, the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and the 6-minute walk test. MLWHFQ was used to assess quality of life[20]. The 6-minute walk test was used to assess exercise tolerance[14]. Evaluation of heart failure symptoms was coded as NYHA functional class.

Response to CRT

Patients were classified as responder when patients showed a decrease of ≥ 15% in left ventricular end systolic volume (LVESV) after 6 months of CRT5. Patients not fulfilling this criterion were classified as non-responders.

Statistics

Results are presented as mean ± SD. Paired or unpaired Student's t-test were used to compare data, when appropriate. A Wilcoxon signed rank test was used to evaluate changes in NYHA class within groups. To determine if BRS has predictive value for the echocardiographic responses to CRT, receiver-operating characteristic (ROC) curve analysis was applied. The ROC curve is a graphical display of trade-offs of the true-positive (sensitivity) and false-positive (1-sensitivity) rates that correspond to each possible discrimination level of the test or variable under consideration: each cut-off level generates a point on the graph. The closer the curve follows the left-hand border and then the top-border of the ROC space, the more accurate the test. The closer the curve comes to the 45 degree diagonal of the ROC space, the less accurate the test. For all tests, a *P*-value < 0.05 was considered significant.

Table 1. *Baseline patient characteristics.*

Sex	27M/6F
Age (years)	66.5 ± 9.5
NYHA class	2.5 ± 0.7
Etiology of cardiomyopathy	
Ischemic	17 (52%)
Non-ischemic	16 (48%)
QRS duration (ms)	157 ± 30
LVEF (%)	157 ± 30
LVEDV (ml)	218 ± 76
LVESV (ml)	159 ± 62
LV dyssynchrony (ms)	57 ± 44
Medication	
ACE inhibitor/AII blocker	31 (94%)
Diuretic	22 (67%)
Spironolactone	18 (55%)
Beta-blocker	29 (88%)
Amiodarone	6 (18%)

Legend to Table 1. LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association.

RESULTS

Study group

Thirty-five CHF patients were included. Two patients were excluded from follow-up (1 patient because of suspected lung cancer, the other because of poor quality of the acoustic window during echocardiography that prevented reliable LVEF assessment), thus leaving 33 subjects in our study group. Thirty of them attended in our previous study[11]. Baseline characteristics of the study group are listed in *Table 1*.

All CRT devices were successfully implanted (Contak Renewal (n=18), Guidant, MN, USA; InSync Sentry (n= 13), Medtronic Inc., MN, USA; Concerto (n= 1), Medtronic Inc., MN, USA; Lumax (n= 1), Biotronic, MI, USA). The atrioventricular delay (AV-delay) was optimized by 2D echocardiography so that it provided the longest filling time for completion of the end-diastolic filling flow before LV contraction (the mean AV-delay was 120 ± 10 ms). No individual adjustments were made to the interventricular delay; the V-V interval was set at 0 ms in all subjects.

Responders and non-responders

After 6 months of CRT, 23 patients (70%) were classified as responders and 10 patients as non-responders (30%), according to the criterion of a decrease of ≥ 15% in LVESV. No deaths occurred during follow-up. There were no significant differences between responders and non-responders in baseline variables (*Table 2*). In responders, substantial reverse remodelling was present, LVEF increased by 34%, left ventricular end diastolic volume (LVEDV) decreased by 16% and LVESV decreased by 28% ($P<0.003$, *Table 2*). In non-responders reverse remodelling did not occur; changes over time in LVEF, LVEDV and LVESV were limited and not statistically significant (*Table 2*). Responders and non-responders both significantly improved in NYHA class and 6-minute walk test, after 6 months of CRT (*Table 2*). In neither of the groups there was a significant change in MLWHFQ.

Table 2. *Clinical and echocardiographic outcome measures in responders and non-responders.*

	Responders		**Non-responders**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
LVEF (%)	27.6 ± 5.6	37.1 ± 7.8*	28.5 ± 10.0	29.3 ± 9.6
LVEDV (ml)	209.3 ± 70.9	175.4 ± 57.4*	239.1 ± 70.6	233.1 ± 69.8
LVESV (ml)	154.5 ± 60.2	112.4 ± 46.3*	178.3 ± 57.2	169.2 ± 66.6
NYHA class	2.5 ± 0.7	1.9 ± 0.7*	2.4 ± 0.7	1.8 ± 0.6 *
MLWHFQ	29.2 ± 18.2	21.9 ± 18.7	25.8 ± 18.0	20.4 ± 14.9
6-min walk test	339.7 ± 113.4	392.8 ±111.8*	306.4 ± 62.6	391.3 ± 62.0*

Legend to Table 2. MLWHFQ: Minnesota Living With Heart Failure Questionnaire; NYHA: New York Heart Association; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; 6-min walk test: 6-minute walk test; *: $P< 0.01$ within group.

Baroreflex sensitivity and heart rate variability

No significant differences in BRS (P= 0.59) and HRV (P= 0.89) between responders and non-responders existed at baseline (*Table 3*). In responders, CRT increased BRS considerably (30%) as compared to the non-responders (P=0.02, *Table 3*). CRT also improved HRV in responders (30%, P=0.02), but there was no significant difference with the change in the non-responders (P=0.24, *Table 3*). In non-responders, CRT did not acutely change BRS or HRV (*Table 3*). ROC analysis revealed that the percentual BRS increase had predictive value for the discrimination of responders and non-responders (area-under-the-curve 0.69; 95% CI 0.51-0.87, maximal accuracy 0.70, see *Figure 1*).

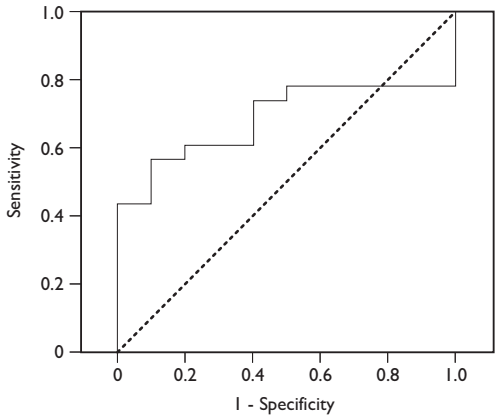

Figure 1. ROC *curve analysis of the predictive value of* CRT*-induced acute* BRS *change for the echocardiographic response to* CRT*. The area-under-the-curve equals 0.69, 95% with a confidence interval of 0.51-0.87.* BRS*: baroreflex sensitivity;* CRT*: cardiac resynchronization therapy.*

DISCUSSION

Response to CRT was defined as echocardiographic reverse remodeling. According to this criterion 70% of our patients were classified as responders and 30% as non-responders. We observed that CRT acutely increased BRS in responders but not in non-responders. ROC curve analysis showed that the CRT-induced acute BRS change at baseline had predictive value for the echocardiographic response to CRT.

A positive effect of CRT on autonomic derangement is not a novel finding per se. In 2006 Sarzi et al.[21] described in a case report that BRS normalized after three months of CRT. Recently, we described an acute positive effect of CRT on BRS[11], while Piepoli et al.[19] demonstrated that BRS and HRV improved with respect to baseline after 12 months of CRT. Also, Burri et al.[8] observed a decrease in sympathetic nerve activity in CRT responders as evidenced by a lowered ^{123}I-MIBG washout. In addition, Najem et al.[17] showed, in clinical responders, that temporarily switching of CRT increased MSNA. These findings suggest that one of the effects of CRT is the reduction of the autonomic derangement associated with CHF. Our current study adds a new element to this, namely the predictive value of a positive autonomic response to CRT for an echocardiographic response, since we demonstrated a positive association between an acute BRS increase after CRT institution and reverse remodelling at mid-term follow-up.

Table 3. *Baseline baroreflex sensitivity and heart rate variability with and without biventricular pacing.*

	Responders		Non-responders	
	CRT off	**CRT on**	**CRT off**	**CRT on**
BRS (mmHg/ms)	2.74 ± 3.7	3.55 ± 4.5*#	3.39 ± 1.6	3.34 ± 1.6
HRV (ms)	18.2 ± 11.0	23.6 ± 15.9*	17.7 ± 3.6	19.2 ± 6.7

Legend toTable 3. BRS: baroreflex sensitivity; CRT: cardiac resynchronization therapy; HRV: heart rate variability (standard deviation of inter-beat intervals); *: P< 0.05 within group; #: P< 0.05 the percentage of change between groups.

The positive association between acute CRT-induced baroreflex improvement and reverse remodelling suggests that the autonomic nervous system is actively involved in reverse remodelling. Possibly, CRT decreases the permanent neurohumoral activation (a hallmark of CHF) by decreasing the involvement of the cardiac sympathetic afferent reflex (CSAR)[8,11]. CSAR is activated by mechanical stretch and by various metabolites which are elevated during myocardial ischemia and with cardiac stretch[18,29]. Improvement of the mechanical activation pattern by CRT may have lowered mechanical stretch[26,31] in part of our patients, and may thus have deactivated CSAR. The arterial baroreflex is known to be suppressed by CSAR[12,32], and the observed baroreflex improvement in part of our study population might well be caused by CRT-induced deactivation of CSAR.

Although sympathoexcitation, possibly induced by cardiac sympathetic afferents, is generally observed in heart failure, cardiac vagal afferents might also play a role in the effects observed in our study. No experiments have been conducted to establish the effect of cardiac vagal afferent stimulation on BRS in the setting of heart failure. In healthy animals, stimulation of cardiac vagal receptors resulted in BRS attenuation[35]. Hence, cardiac vagal afferent firing, like cardiac sympathetic afferent firing, may well inhibit the effect of baroreceptor firing at the level of the nucleus tractus solitarii (NTS). As a consequence, possible CRT-induced decrease of cardiac vagal afferent firing would, like possible CRT-induced decrease of cardiac sympathetic afferent firing, lead to facilitation of the baroreflex. This reasoning would become more complicated when both sympathetic and vagal afferents are involved, because it was reported that major part of these fibers have an occlusive interaction at the NTS[28].

In addition to baroreflex improvement, one would also expect improvement (decrease) in the neurohormone levels. Unfortunately, little research has been conducted about the effects of CRT on neurohormone levels, and the results reported in the literature are inconsistent[6,7,15,24]. We have not systematically measured neurohormone plasma levels in our study population, hence, a positive association between a positive BRS response to CRT and normalization of the neurohormone levels remains hypothetical.

An echocardiographic outcome for evaluation of the response to CRT was chosen, since it is a robust measure and less subject to both the patient's and clinician's interpretation then clinical outcome variables[1,5]. A limitation of this outcome variable is that there are clinical responders that exhibit a decrease of >15% in LVESV, these patients were not indicated as responder in our study. However, Yu et al.[34] showed that clinical outcome variables did not predict mortality, more over, LVESV was the only independent predictor of all cause mortality. Also Ypenburg et al.[33] found that long-term prognosis after CRT is related to the extend of left ventricular reverse remodeling at 6 months of follow-up.

Obviously, the predictive value of the CRT-induced acute BRS change can not be used to reduce the number of CRT implantations in those who appear to become non-responders. The clinical use of our findings would rather lie in additional attempts to adjust the pacemaker settings in expected non-responders to CRT (subjects not showing an acute BRS increase).

Currently A-V optimization is recommended over V-V optimization[25]. If an acute positive BRS change is predictive for a positive response to CRT, it could be considered to attempt V-V optimization in cases where an acute BRS increase does not occur. To maximize the beneficial effect of CRT by means of V-V optimization, aiming for the largest BRS might prove as valuable as the assessment of

pulsed-wave Doppler measurements over the LV outflow tract. Of course, the usefulness of such a procedure has to be demonstrated in a prospective study.

Obviously, the limited size of our study group opposes a limitation to the statistical armament suitable for analysis of the data. For a larger group, a multivariate logistic regression would have been appropriate, thus controlling for major confounders like age, sex, heart failure severity (NYHA class), ejection fraction, etc. For our relatively small group we have chosen for a simple ROC analysis, that unlike regression analysis, does not model the data but straightforwardly uses the original data for the computation of the confidence interval. To further corroborate the results of our study, a larger study group is needed, thus allowing to control for major confounders.

CONCLUSIONS

The current results demonstrated that the CRT-induced acute BRS increase has predictive value for the anatomical response (reverse remodelling) to CRT. The present findings underscore the relevance of the autonomic nervous system as an effect pathway/mechanism of CRT in CHF.

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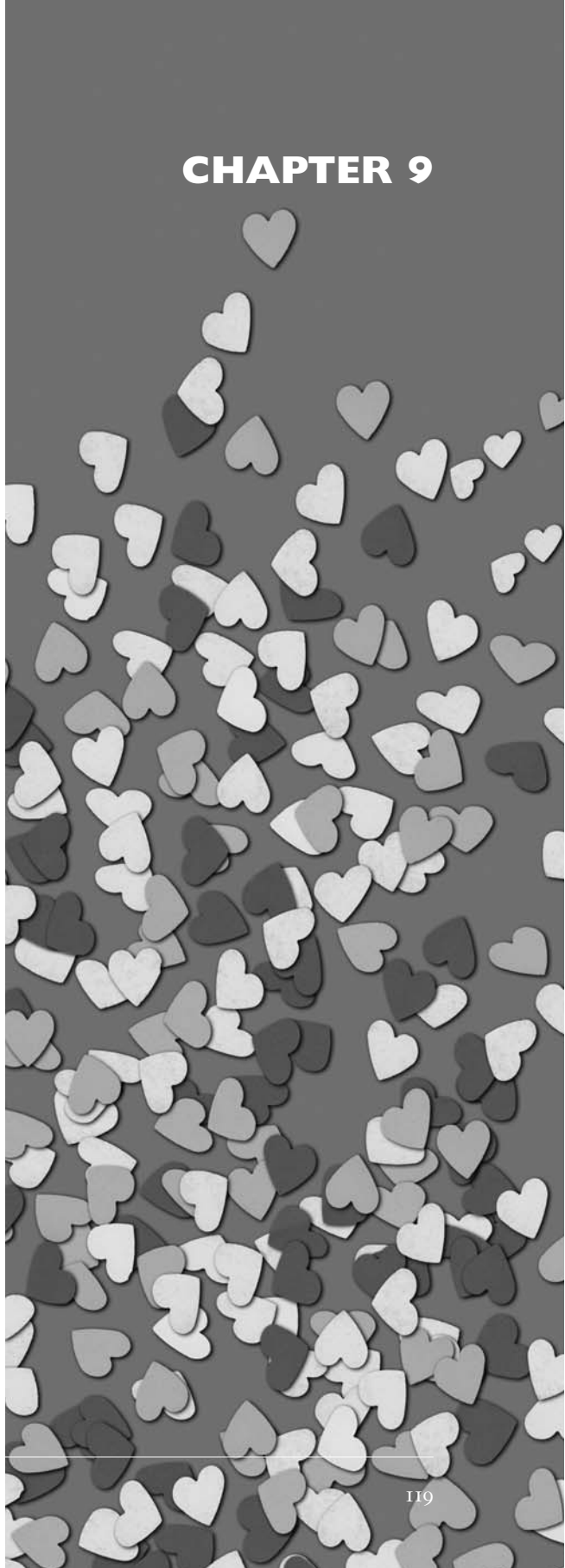
CHAPTER 9



SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEF

SUMMARY

Aim of the research described in this thesis was to investigate the effects of exercise training and of biventricular pacing on fitness-related variables in the setting of chronic heart failure (CHF). The studied variables were results of cardiopulmonary exercise testing analysis and baroreflex sensitivity (BRS). Also, we addressed the underlying mechanisms.

In *Chapter 2* we reviewed the effects of exercise training on neurohumoral excitation and autonomic derangement at rest. We concluded that exercise training increases BRS and heart rate variability (HRV) and reduces sympathetic outflow, plasma levels of catecholamines, angiotensin II, vasopressin and brain natriuretic peptides at rest. Data on the effect of exercise training on endothelin and aldosteron levels at rest were not conclusive.

In *Chapter 3* we addressed, in a modeling study, a number of issues that are relevant for the interpretation of BRS. By means of computer simulations we investigated the link between the well known phenomenon of blood pressure resonance (the Mayer waves) on one hand, and blood pressure buffering (the essential function of the baroreflex) on the other hand. Simulations were done with various randomly chosen combinations of feedback gains in the parasympathetic and sympathetic baroreflex arms to the heart and to the peripheral vasculature. Output variables were: blood pressure resonance amplitude, blood pressure buffering capacity, and BRS. We found that high blood pressure resonance amplitude was associated with better blood pressure buffering capacity. BRS is almost uniquely determined by the vagal baroreflex gain to the sinus node. In conclusion, blood pressure buffering and BRS are unrelated unless coupled gains in all baroreflex limbs are assumed.

As CHF patients have low exercise capacity and, hence, the assessment of efficient and effective rehabilitation programs is difficult, insight in the currently unknown mechanism by which the training effect of exercise on BRS is mediated is of utmost importance. Therefore, in *Chapter 4*, we investigated if an increase in BRS could also be achieved by an alternative protocol. We compared, in stable untrained CHF patients, the effect of transcutaneous electrical nerve stimulation (TENS) with the effects of bicycle exercise training. By applying TENS in the form of periodic (2/s, marching pace) burst stimulation to the feet, we attempted to mimic an exercise-associated somatosensory ergoreceptor stimulation pattern. TENS and exercise training sessions were held during two successive days. BRS, measured noninvasively prior to the first intervention session (baseline) and one day after the second intervention session (training effect), increased significantly in the TENS group, but did not change in the exercise training group. Hence, we demonstrated that periodic somatosensory input alone, *i.e.*, without actual exercise, is sufficient and efficient in improving the arterial baroreflex in CHF patients. Two sessions of TENS were even more effective than two boots of exercise; this observation is likely due to the inability of CHF patients to exercise at a level at which there is sufficiently intense afferent somatosensoric nerve traffic. This concept may therefore, constitute a basis for more effective exercise training regimens in the diseased/impaired, in whom training should focus more on the somatosensory component of exercise than on the intensity of exercise.

In addition to improve autonomic nervous system functioning, it is also important to improve exercise capacity, as the degree of exercise intolerance in CHF is paralleled by an increased mortality, and several studies suggest that increasing exercise capacity in CHF improves prognosis. In *Chapters 5* and *6* we investigated whether exercise training, besides peak oxygen uptake ($\dot{v}O_{2\,peak}$) and $\dot{v}E/\dot{v}CO_2$slope, also improved the oxygen uptake efficiency slope (OUES) and the oxygen uptake-work relationship ($\Delta\dot{v}O_2/\Delta w$). In contrast to the maximal oxygen uptake, OUES and $\Delta\dot{v}O_2/\Delta w$ are independent of the maximally attained exercise intensity. In both studies we compared a non-exercising control group with an exercise training group; both groups consisted of CHF patients eligible for rehabilitation. OUES and $\Delta\dot{v}O_2/\Delta w$ were measured during a symptom limited exercise test, which was performed at baseline and repeated after four weeks (in the control group) or after completion of a training program (in the exercise training group). We found that exercise training increased OUES. In 58% of our population $\Delta\dot{v}O_2/\Delta w$ baseline values were normal. In patients with decreased $\Delta\dot{v}O_2/\Delta w$, exercise training improved $\Delta\dot{v}O_2/\Delta w$. However, as all exercise testing parameters reflect different aspects of the cardiopulmonary system during exercise, we think it is of importance to assess $\Delta\dot{v}O_2/\Delta w$ in combination with other cardiopulmonary exercise training variables like $\dot{v}O_{2\,peak}$, $\dot{v}E/\dot{v}CO_2$ slope and OUES, as a measure of CHF severity, or as an evaluation tool for exercise training programs.

In *Chapter 7* and *Chapter 8* we studied the effect of biventricular pacing on the arterial baroreflex. Metabolic and mechanical stress in the failing heart activates the cardiac sympathetic afferent reflex (CSAR) even at rest. It has been demonstrated that in clinical responders muscle sympathetic nerve activity (MSNA) acutely increases after switching of the cardiac resynchronization therapy (CRT) device. Therefore it seems that CRT decreases MSNA. Mechanistically, this beneficial effect might be explained by acute deactivation of the CSAR. Since CSAR afferent firing decreases arterial BRS[7,13], CRT-induced CSAR deactivation is likely accompanied by a BRS increase. In *Chapter 7* we studied the acute effect of biventricular pacing on the arterial baroreflex. One day after implantation of a CRT device in CHF patients we measured BRS and HRV under two conditions: CRT device switched-on and switched-off (on/off order randomized). CRT acutely increased BRS and HRV. This favorable response of the autonomic nervous system may be caused by CRT induced CSAR deactivation.

In *Chapter 8* we hypothesized that the acute response in BRS after institution of CRT has predictive value for mid-term anatomical response (reverse remodeling). Echocardiography was performed prior to implantation (baseline) and 6 months after implantation (follow-up). CRT responders were defined as patients in whom left ventricular end systolic volume had decreased by ≥ 15% at follow-up[2,14]. In responders, but not in non-responders, CRT increased BRS and HRV at baseline. Receiver operating characteristic (ROC) curve analysis revealed that the percentual BRS increase had predictive value for the discrimination of responders and non-responders (area-under-the-curve 0.69; 95% confidence interval 0.51-0.87; maximal accuracy 0.70). Hence, we demonstrated that a CRT-induced acute BRS increase at baseline has predictive value for the echocardiographic response to CRT. This finding suggests that the autonomic nervous system is actively involved in CRT-related reverse remodeling.

CONCLUSIONS

- Exercise training increases baroreflex sensitivity and reduces sympathetic outflow, plasma levels of catecholamines, angiotensin II, aldosteron, vasopressin and atrial natriuretic peptides at rest
- Baroreflex mediated blood pressure buffering and baroreflex sensitivity are unrelated unless coupled gains in all baroreflex limbs are assumed
- Periodic somatosensory stimulation increases arterial baroreflex sensitivity in chronic heart failure patients
- Exercise training in CHF patients increases the oxygen uptake efficiency slope
- In CHF patients with decreased $\Delta\dot{v}o_2/\Delta w$ exercise training improves $\Delta\dot{v}o_2/\Delta w$
- Cardiac resynchronization therapy acutely increases baroreflex sensitivity
- An acute increase of baroreflex sensitivity upon institution of biventricular pacing has predictive value for the anatomical response to cardiac resynchronization therapy

FUTURE PERSPECTIVES

Exercise training

In daily practice, $\dot{v}o_{2\,peak}$ is the most frequently used variable for the evaluation of exercise capacity of heart failure patients. However, the interpretation of $\dot{v}o_{2\,peak}$ is difficult because it depends on the motivation of patient and test leader, and on the selected exercise testing protocol[1,12]. Therefore, in CHF, exercise testing variables are to be preferred that can be obtained from submaximal exercise data. E.g., OUES, $\dot{v}E/\dot{v}CO_2$ slope and $\Delta\dot{v}o_2/\Delta w$ can easily be computed from respiratory gas exchange results obtained during the test, and have important prognostic value[4,5]. Meaningful results can already be derived from the data generated during the lower 75% of the covered exercise intensity range[6,8,9]. Also, in this thesis we showed that these exercise testing variables are sensitive enough to measure exercise training-induced changes. We are of the opinion that assessing all mentioned exercise testing variables together for each individual will make it possible to establish a more reliable representation of the patient's individual capabilities and drawbacks. Also, exercise testing variables have all important prognostic value[5,10] and, combining these variables may constitute an important powerful prognostic tool. Hence, it would be a step forward if all mentioned exercise testing variables would routinely be computed before starting and after completion of a rehabilitation program as objective measurements of the achieved rehabilitation effect.

We demonstrated that exercise training improves OUES and $\Delta\dot{v}o_2/\Delta w$. In addition, in a literature study, we found that exercise training improves autonomic functioning in CHF. However, the prognostic value of these findings remain unknown. Therefore, follow-up studies are needed to demonstrate if improvements of these variables induced by exercise training are associated with improved prognosis. Also the association between the improvement in cardiopulmonary exercise testing variables and autonomic functioning in CHF is not clear. This association is of utmost importance, as currently exercise training programs focus primarily on increasing exercise capacity and not on improving autonomic functioning. Furthermore, to develop efficient training programs in CHF, the mechanism by which exercise training normalizes autonomic derangement and neurohumoral activation needs further elucidation. As an increase in BRS improves prognosis, measurement of BRS at baseline and after completion the rehabilitation program would also provide an objective and meaningful rehabilitation effect.

In this thesis we found indications that somatosensory information is one of the mechanisms through which exercise training normalizes autonomic functioning. If true, we would also expect that such somatosensory information decreases neurohumoral activation. Currently, we are completing a randomized controlled trial (the ALLEGRO study) to confirm our findings. In the ALLEGRO study we compare the effects of exercise training and periodic somatosensory stimulation by TENS to a control group during an intervention period of two weeks. In addition to BRS, outcome measures are cardiopulmonary exercise testing variables, six minute walk test, Minnesota Living With Heart Failure Questionnaire and several blood parameters that reflect the amount of neurohumoral activation (norepinephrine, epinephrine, NT-proBNP, plasma renin activity and aldosteron). The ALLEGRO study has both practical and theoretical importance. If the hypothesis is true that periodic somatosensory stimulation decreases neurohumoral activation, patients with any form of exercise intolerance could gain benefit from light but rhythmic activity.

Biventricular pacing

In this thesis we provided suggestive evidence that the acute CRT-induced BRS response is caused by CSAR deactivation. If true, this would be an important finding as chronic CSAR firing is one of the causes of the permanent sympathoexcitation in CHF. Moreover, it seems that CSAR, in addition to a generalized sympathoexcitatory effect, also has a preferential sympathoexcitatory effect on the heart itself[11]. Excessive sympathoexcitation in the heart increases electrical instability, and high catecholamine concentrations may be toxic to cardiomyocytes[3]. As recording of CSAR afferent activity is currently not possible in humans in vivo, new animal studies are needed to determine whether the CRT-induced BRS increase is indeed caused by CSAR deactivitation.

In this thesis we have shown that both exercise training and biventricular pacing increase fitness in CHF patients. The mechanisms causing this effect are still unknown, hence studies are needed to elucidate these mechanisms. Also, studies that address the potential prevention capabilities of exercise training and of biventricular pacing are needed, as once heart failure has developed the underlying process cannot be reversed. With regard to CRT, 'early' application is still a dilemma (high risk and costs), but for exercise training is this not the case as physical training is accepted as primary prevention of cardiovascular disease. The question is if exercise training in populations with a high risk of heart failure, for instance patients with a history of myocardial infarction, should be implemented in the therapeutic regimen, next to standard pharmacological therapy, to prevent or to delay the development of heart failure.

SAMENVATTING

Bij een hartfalenpatiënt in rust vertoont het bloed, paradoxalerwijs, een beeld van voortdurende excitatie van zowel het autonome zenuwstelsel als van de regelsystemen, die vocht en zout in het lichaam vasthouden en samentrekking van de bloedvaten veroorzaken. Dit wordt samengevat met de term 'neurohumorale activatie'. Deze regelsystemen komen bij gezonde personen slechts in actie om stressoren te kunnen weerstaan en de vochtbalans te handhaven. Permanente activatie van deze regelsystemen bij hartfalenpatiënten heeft op termijn zeer nadelige effecten op het hart. De huidige therapie is er bij hartfalenpatiënten voornamelijk op gericht om de invloed van de neurohumorale activatie medicamenteus te blokkeren, maar niet om de neurohumorale activatie weg te nemen.

De neurohumorale activatie bij hartfalenpatiënten gaat samen met een verslechtering van de arteriële baroreflex. De arteriële baroreflex dempt schommelingen in de bloeddruk en is derhalve een beschermende reflex. De baroreflex compenseert bijvoorbeeld voor bloeddrukverhoging bij een stressor door middel van een toename van de parasympathische outflow en afname van sympathische outflow naar het hart, samen met een afname van de sympathische outflow naar de bloedvaten in het hele lichaam. Hierdoor zullen de hartfrequentie, de contractiliteit van het hart en de perifere weerstand dalen en als gevolg hiervan zal de bloeddruk dalen. De sterkte van deze reflex wordt vaak uitgedrukt in de baroreflex sensitiviteit (BRS). De hoogte van de BRS heeft een sterke voorspellende waarde in hartfalenpatiënten.

Hartfalenpatiënten hebben tevens een verlaagde inspanningscapaciteit. Ook dit is een gevolg van de neurohumorale activatie. De bloedvaten zullen bijvoorbeeld door deze neurohumorale activatie samentrekken waardoor er minder zuurstof naar de werkende spieren vervoerd kan worden. De verlaagde inspanningscapaciteit beperkt hartfalenpatiënten in hun dagelijkse activiteiten. De mate waarin de inspanningscapaciteit verlaagd is heeft voorspellende waarde voor de mortaliteit. Verschillende onderzoeken geven aan dat een verbetering van de inspanningscapaciteit de prognose van hartfalenpatiënten ook verbetert. Het is dus belangrijk om naast het terugdringen van de neurohumorale activatie en het verbeteren van de BRS ook de inspanningscapaciteit bij hartfalenpatiënten te verbeteren.

Het doel van dit proefschrift was om de effecten van lichamelijke inspanning en van biventriculair pacen op fitness gerelateerde variabelen in de setting van hartfalen te bestuderen. In dit proefschrift hebben we ons op twee verschillende aspecten van fitness gericht die voor hartfalenpatiënten relevant zijn: de fysieke fitness (inspanningscapaciteit) en de fitness van het autonome zenuwstelsel (de neurohumorale activatie en de BRS). Wanneer een hartfalenpatiënt een hoge autonome fitness heeft wil dit dus zeggen dat de BRS hoog is en er weinig neurohumorale excitatie in rust aanwezig is. Daarnaast hebben we ook de onderliggende effectmechanismen van de gunstige veranderingen die teweeggebracht worden door lichamelijke inspanning en door biventriculair pacen aan de orde gesteld.

In *hoofdstuk 2* beschrijven we, in een overzichtsartikel, de effecten van lichamelijke inspanning op de neurohumorale excitatie en autonome ontregeling in rust. Wij concluderen dat fysieke training de BRS en de hartritme variabiliteit (HRV) verbetert. Daarnaast vermindert fysieke training de sympathische outflow en de bloedplasma concentraties van catecholaminen, angiotensine II, vasopressine en BNP. Wij kunnen geen conclusies trekken over de effecten van lichamelijke inspanning op de endotheline en aldosteron concentraties in het bloedplasma.

In *hoofdstuk 3* hebben we met behulp van computersimulaties bestudeerd wat de relatie is tussen 1) de BRS als index voor de baroreflex functie, 2) de mate waarin de baroreflex fluctuaties in de bloeddruk dempt, en 3) de mate waarin de baroreflex door resonantie juist fluctuaties in de bloeddruk opwekt. De baroreflex gaat veranderingen in de bloeddruk tegen, maar het duurt enige seconden voor (bijvoorbeeld) een bloeddrukstijging ook daadwerkelijk door de baroreflex is gedempt. Veel regelsystemen hebben een looptijd tussen afwijking en regeleffect, en het is een gegeven uit de cybernetica dat dit bij bepaalde frequenties van de verstoring juist resonantie kan veroorzaken, waardoor de oorspronkelijke verstoring versterkt wordt in plaats van verzwakt. De resonantiefrequentie van de baroreflex geregelde bloeddruk bevindt zich in de buurt de 0.1 Hz, het bekende '10-seconden ritme' in de bloeddruk, ofwel de Mayer waves. Onze computersimulaties geven aan dat er een verband is tussen de grootte van de Mayer waves en de mate waarin een veel langzamere verandering in de bloeddruk door de baroreflex gedempt wordt. Daarnaast laten onze simulaties zien dat het mogelijk is om betrouwbaar de BRS te meten in het frequentiegebied van de bloeddrukresonantie. Ook geven onze simulaties aan dat een grote BRS geen aanleiding geeft tot veel resonantie in de bloeddruk. Eerder hangt een hoge waarde van de BRS samen met het hebben van veel HRV, die geassocieerd is met een sterke, parasympathisch bepaalde, via de vagus zenuw binnenkomende beïnvloeding van het hart. Deze bevinding suggereert dat een belangrijk deel van de gunstige prognose die met een hoge BRS samenhangt verklaard zou kunnen worden door een sterkere vagale feedback naar het hart op momenten van fysieke of mentale belasting.

Het is belangrijk om inzicht te verkrijgen in het achterliggende mechanisme van het fysieke trainingseffect op de baroreflex aangezien de lage inspanningscapaciteit van hartfalenpatiënten een belemmering is om intensieve revalidatie programma's aan te kunnen. In *hoofdstuk 4* hebben we onderzocht of een verbetering in de BRS ook bereikt kon worden door middel van periodieke somatosensorische stimulatie. De gedachte hierachter is dat er nu eenmaal voor de hersenstam een aanleiding moet zijn om de gain van de baroreflex bij te stellen. De vraag is dan hoe de hersenstam 'weet' dat er lichamelijke activiteit gaande is. Hoogstwaarschijnlijk komt deze informatie in de hersenstam door zenuwverkeer afkomstig uit de spieren waarmee arbeid verricht wordt. Omdat activiteiten, zoals lopen en fietsen, een ritme hebben, valt te verwachten dat de hersenstam periodieke somatosensorische informatie als zodanig herkent en overeenkomstig zal reageren. We hebben bij hartfalenpatiënten het effect van TENS (transcutane elektrische neuro stimulatie) vergeleken met het effect van fietstraining. We hebben TENS in de vorm van periodieke stimulatie (2 bursts per seconde, loop ritme) op de voeten aangebracht. Op deze manier hebben we geprobeerd om het ergoreceptor zenuwverkeer dat gedurende inspanning bestaat na te bootsen. Zowel de TENS- als de fietstraining sessies werden op twee opeenvolgende dagen gehouden. De BRS, gemeten voor de eerste interventie sessie (uitgangssituatie) en een dag na de tweede interventie sessie (trainingseffect), verbeterde significant in de TENS groep, maar veranderde niet in de fietstraining groep. We hebben hiermee aangetoond dat periodieke somatosensorische input in staat is om de arteriële baroreflex in hartfalenpatiënten te verbeteren. TENS leek zelfs effectiever dan fietstraining, dit kan worden verklaard door het feit dat hartfalenpatiënten zich niet kunnen inspannen op het niveau waarbij afferent somatosensorisch zenuwverkeer met voldoende intensiteit ontstaat. In de vorm van TENS kon dat zenuwverkeer wel met voldoende intensiteit worden gerealiseerd (en verdragen). De gedachte dat periodieke somatosensorische informatie een belangrijke component in het verbeteren van de BRS is, kan een basis vormen voor meer effectieve trainingsvormen bij zieken/gehandicapten. In deze patiëntenpopulatie zal het accent van fysieke training meer moeten liggen op de somatosensorische component van inspanning dan op de inspanningsintensiteit, met andere woorden: de aandacht zou dan moeten verschuiven van de vraag hoe de belastbaarheid van de patiënt kan

worden opgevoerd naar de vraag hoe de patiënt het beste periodieke somatosensorische stimuli van voldoende intensiteit kan verkrijgen, of, anders geformuleerd, welke bewegingsvorm rijk is aan somatosensorische stimulatie, terwijl dit verhoudingsgewijs weinig inspanning kost.

Aangezien bij patiënten met hartfalen een verminderde inspanningstolerantie samengaat met een verhoogde mortaliteit is het, naast het verbeteren van de autonome fitness, ook van belang de inspanningscapaciteit te verbeteren. Verschillende onderzoeken geven namelijk aan dat het verbeteren van de inspanningscapaciteit, of afgeleiden hiervan, de prognose van hartfalenpatiënten verbetert. In *hoofdstuk 5* en *6* hebben we onderzocht of fysieke training naast de piek zuurstofopname ($\dot{V}O_{2\,piek}$) en de $\dot{V}E/\dot{V}CO_2$helling, ook de 'oxygen uptake efficiency slope' (OUES) en de zuurstof opname-arbeid relatie ($\Delta\dot{V}O_2/\Delta W$) verbetert. Bij hartfalenpatiënten was dit nog niet bekend. De nu meest gebruikte maat voor de inspanningscapaciteit bij hartfalenpatiënten is de $\dot{V}O_{2\,piek}$, deze is echter lastig te interpreteren, aangezien deze afhankelijk is van de motivatie van patiënt en testleider, en ook van het gekozen inspanningstest protocol. In tegenstelling tot de $\dot{V}O_{2\,piek}$, kunnen de OUES en de $\Delta\dot{V}O_2/\Delta W$ uit submaximale inspanningsdata berekend worden en zijn dus onafhankelijk van de maximaal behaalde inspanningsintensiteit. Daardoor kunnen deze maten betrouwbaarder in hartfalenpatiënten gemeten worden.

In beide onderzoeken hebben we een niet-actieve controlegroep met een trainingsgroep vergeleken. Beide groepen bestonden uit stabiele hartfalenpatiënten die op het punt stonden om met een revalidatieprogramma te beginnen. De trainingssessies bestonden uit een duurtraining-gedeelte, waarin gefietst werd en een krachttraining-gedeelte, waarin lichte krachtoefeningen plaatsvonden. OUES en $\Delta\dot{V}O_2/\Delta W$ werden gemeten door middel van een fietsergometrie-test. Deze werd uitgevoerd voor de aanvang van het revalidatieprogramma en herhaald na vier weken (in de controle-groep) of na het afsluiten van het trainingsprogramma (in de fysieke trainingsgroep). Het trainingsprogramma verbeterde de OUES. De helft van onze onderzoekspopulatie had normale $\Delta\dot{V}O_2/\Delta W$ waarden bij aanvang, het trainingsprogramma had bij deze patiënten begrijpelijkerwijs geen effect op de $\Delta\dot{V}O_2/\Delta W$. Bij patiënten met een verminderde $\Delta\dot{V}O_2/\Delta W$ verbeterde de training deze waarde. Aangezien niet alle patiënten een verminderde $\Delta\dot{V}O_2/\Delta W$ hebben, zou men zich kunnen afvragen of het wel zinvol is om deze variabele te bepalen. De $\Delta\dot{V}O_2/\Delta W$ is echter gerelateerd aan de ernst van het hartfalen. Ook behelzen de verschillende inspanningscapaciteit variabelen verschillende aspecten van de bij inspanning betrokken systemen, zoals het hart, de longen, de bloedvaten en de skeletspieren. We zijn dan ook van mening dat het belangrijk is om de $\Delta\dot{V}O_2/\Delta W$ in combinatie met andere cardiopulmonale inspanningscapaciteit variabelen zoals $\dot{V}O_{2\,peak}$, $\dot{V}E/\dot{V}CO_2$ slope en OUES te meten om de effectiviteit van trainingsprogramma's bij patiënten met hartfalen beter te kunnen beoordelen. Op deze wijze ontstaat er per patiënt een individueel beeld van de door training teweeggebrachte veranderingen.

In de *hoofdstukken 7* en *8* hebben we het effect van cardiale resynchronisatie therapie (CRT) op de arteriële baroreflex bestudeerd. In het falende hart wordt de cardiale sympathische afferente reflex (CSAR) permanent (dus ook in rust) door zowel metabole als mechanische stress geactiveerd. Hier uit volgt dat CSAR activatie een van de oorzaken van de permanente sympathische outflow in hartfalenpatiënten. Uit een eerder onderzoek is gebleken dat bij tijdelijk uitschakelen van het CRT-device (biventriculaire pacemaker) bij patiënten, die positief op deze behandeling reageerden (klinische responders), de 'muscle sympathetic nerve activity' direct toenam. Mechanistisch zou dit effect verklaard kunnen worden doordat CRT direct de CSAR beïnvloedt. CRT vermindert de mechanische stress in de hartwand waardoor de CSAR activiteit zou kunnen dalen. Het is bekend dat CSAR activatie de BRS verlaagt[7,13].

Derhalve zal een CRT geïnduceerde verminderde CSAR activiteit waarschijnlijk gepaard gaan met een verbetering in BRS.

In *hoofdstuk 7* hebben we het acute effect van CRT op de arteriële baroreflex bestudeerd. Een dag na de implantatie van een CRT-device werd bij hartfalenpatiënten de BRS en HRV in twee verschillende modaliteiten gemeten: CRT-device aan en CRT-device uit (de aan/uit volgorde was gerandomiseerd). BRS en HRV verbeterden acuut bij het aanzetten van de CRT. We hebben geen andere verklaring voor deze gunstige respons van het autonome zenuwstelsel dan dat deze wordt veroorzaakt door CRT-geïnduceerde CSAR deactivatie.

In *hoofdstuk 8* hebben we onderzocht of de acute verandering in BRS bij baseline, na het aanzetten van het CRT-device, voorspellende waarde had voor de anatomische respons ('reverse remodeling') op CRT na de zes maanden. Voorafgaande aan de implantatie en 6 maanden na de implantatie werd een echocardiogram gemaakt. Een vermindering van het linker ventrikel eind-systolisch volume van ≥ 15% na 6 maanden CRT therapie werd beschouwd als een positieve anatomische respons[2,14]. Bij anatomische responders was bij baseline de BRS groter met de biventriculaire pacemaker aan dan met de biventriculaire pacemaker uit. Dit was niet het geval bij patiënten waarbij CRT na 6 maanden geen anatomische respons was opgetreden. 'Receiver-operating curve' (ROC) analyse liet zien dat de door CRT veroorzaakte procentuele BRS verbetering bij baseline voorspellende waarde had voor de anatomische respons op CRT (oppervlakte onder de curve 0.69; 95% betrouwbaarheidsinterval 0.51–0.87; maximale nauwkeurigheid 0.70). We hebben dus aangetoond dat een door CRT geïnduceerde acute verbetering van de BRS bij baseline voorspellende waarde heeft voor de anatomische respons na 6 maanden CRT. Deze bevinding suggereert dat het autonome zenuwstelsel actief betrokken is bij de 'reverse remodeling' die als gevolg van CRT plaatsvindt.

CONCLUSIES

- Lichamelijke inspanning vergroot de baroreflex sensitiviteit en vermindert de sympathische excitatie en de bloedplasma concentraties van catecholaminen, angiotensine II, aldosteron, vasopressine en ANP in rust
- De bloeddruk buffering capaciteit en de BRS zijn alleen aan elkaar gerelateerd als aangenomen wordt dat de gains in alle efferente baroreflex armen gekoppeld zijn
- Periodieke somatosensorische stimulatie bij hartfalenpatiënten verbetert de arteriële baroreflex
- Lichamelijke inspanning verbetert de 'oxygen uptake efficiency slope' bij hartfalenpatiënten
- Bij hartfalenpatiënten met een verminderde $\Delta\dot{V}O_2/\Delta W$ verbetert lichamelijke inspanning deze $\Delta\dot{V}O_2/\Delta W$
- Cardiale resynchronisatie therapie verbetert acuut de baroreflex sensitiviteit
- Een acute door biventriculaire pacing veroorzaakte verbetering in baroreflex sensitiviteit heeft voorspellende waarde voor de anatomische respons op cardiale resynchronisatie therapie

TOEKOMSTPERSPECTIEVEN

Fysieke training

In de dagelijkse praktijk is de $\dot{V}O_{2\,piek}$ de meest gebruikte maat bij de evaluatie van de inspanningscapaciteit van hartfalenpatiënten. Echter, de behaalde $\dot{V}O_{2\,piek}$ is lastig te interpreteren, omdat deze afhankelijk is van de motivatie van patiënt en testleider, alsmede van het gekozen inspanningstest protocol[1,12]. Derhalve verdienen inspanningstestvariabelen die verkregen worden uit de data van een submaximale inspanningstest, die dus niet afhankelijk zijn van bovengenoemde factoren, de voorkeur. De OUES, de $\dot{V}E/\dot{V}CO_2$ helling en $\Delta\dot{V}O_2/\Delta W$, die belangrijke prognostische waarde hebben, kunnen gemakkelijk berekend worden uit de respiratoire gasanalyse data die gedurende een fietstest verkregen worden[4,5]. Resultaten hiervan kunnen al worden afgeleid uit de gegevens afkomstig van de onderste 75% van de totaal doorlopen inspanningsintensiteit range[6,8,9]. In dit proefschrift hebben we laten zien dat deze inspanningstestvariabelen gevoelig genoeg zijn om veranderingen na een trainingsprogramma aan te tonen. Wanneer alle hiervoor genoemde inspanningstestvariabelen per individu bepaald zouden worden, wordt het mogelijk om een meer betrouwbare representatie van de individuele capaciteiten en tekortkomingen per patiënt te verkrijgen. Het is een stap voorwaarts zijn als alle genoemde inspanningstestvariabelen zouden worden berekend als objectieve meting van het behaalde revalidatie effect. Daarnaast hebben deze inspanningstestvariabelen een aangetoonde prognostische waarde[5,10] en een combinatie van deze variabelen zal wellicht in de toekomst als belangrijk prognostisch instrument kunnen dienen.

We hebben aangetoond dat fysieke training zowel de inspanningscapaciteit (OUES en $\Delta\dot{V}O_2/\Delta W$) als de autonome fitness in hartfalenpatiënten verbetert. De prognostische waarde van deze bevindingen is echter onbekend. Vervolgonderzoek is nodig om te bepalen of de door fysieke training geïnduceerde verbeteringen ook leiden tot een verbeterde prognose. Tevens is de associatie tussen de verbetering in cardiopulmonale inspanningstestvariabelen en het functioneren van het autonome zenuwstelsel bij hartfalenpatiënten onduidelijk. Deze associatie is zeer belangrijk, daar fysieke trainingsprogramma's zich voornamelijk richten op het verbeteren van de inspanningscapaciteit en niet zozeer op het verbeteren van het autonoom functioneren. Bovendien moet, om voor hartfalenpatiënten efficiënte trainingsprogramma's te kunnen ontwikkelen, het mechanisme achterhaald worden waardoor training de autonome verstoring en de neurohumorale activatie terugdringt. Aangezien een verhoging van de BRS de prognose verbetert, zou de meting van de BRS aan het begin en na het beëindigen van een revalidatieprogramma een objectief en belangrijk revalidatie effect ten aanzien van de werking van het autonome zenuwstelsel kunnen weergeven.

Het in dit proefschrift beschreven onderzoek heeft aanwijzingen opgeleverd dat somatosensorische informatie een van de onderliggende stimuli is door middel waarvan fysieke training het functioneren van het autonome zenuwstelsel normaliseert. Als dit werkelijk zo is, dan kan ook humorale normalisatie (normalistatie van de catecholamine, aldosteron, renine, en NT-proBNP concentraties in het bloed) als respons op deze stimulus verwacht worden. Op dit moment sluiten we een gerandomiseerd gecontroleerd onderzoek (de ALLEGRO studie) af dat opgezet was om deze hypothese te onderzoeken. In de ALLEGRO studie vergelijken we effecten van behandeling door fysieke training en door middel van TENS toegediende somatosensorische stimuli met een niet actieve controle groep gedurende een interventieperiode van twee weken. In de ALLEGRO studie worden de volgende uitkomstvariabelen onderzocht: de BRS, diverse bloed parameters (norepinephrine, epinephrine, NT-proBNP, plasma renine activiteit and aldosteron), de zes-minuten wandeltest, cardiopulmonale inspanningstestvariabelen en kwaliteit van leven. De ALLEGRO studie is van zowel praktisch als theoretisch belang. Als de hypothese, dat periodieke somatosensorische stimulatie de neurohumorale activatie vermindert en de BRS verbetert klopt, dan zouden patiënten met een lage inspanningstolerantie immers kunnen profiteren van lichte, maar wel ritmische activiteit.

Cardiale resynchronisatie therapie

In dit proefschrift hebben we gepostuleerd dat de acute door CRT geïnduceerde verandering in BRS veroorzaakt wordt door CSAR deactivatie. Als dit waar blijkt te zijn, is dat een belangrijke bevinding, omdat chronische CSAR activatie een van de oorzaken van de permanente neurohumorale excitatie in hartfalen is. Bovendien lijkt het er op dat CSAR, naast gegeneraliseerde sympathicus excitatie, ook nog preferentiële sympathische excitatie van het hart veroorzaakt[11]. Buitensporige sympathische excitatie van het hart veroorzaakt elektrische instabiliteit (ritmestoornissen), ook zijn hoge catecholamineconcentraties toxisch voor cardiomyocyten[3]. Aangezien het nog niet mogelijk is om in mensen de activiteit van cardiale afferenten te meten, is proefdieronderzoek nodig om te bepalen of CSAR deactivitatie een van de oorzaken is voor de door CRT veroorzaakte acute BRS verbetering.

In dit proefschrift hebben we laten zien dat zowel fysieke training als CRT in staat zijn om de autonome fitness (het goed werken van het autonome zenuwstelsel/de arteriële baroreflex) van hartfalenpatiënten te verbeteren. De mechanismen die deze effecten veroorzaken, zijn nog niet bekend. Er is dan ook onderzoek nodig om de onderliggende mechanismen te achterhalen die de positieve effecten van fysieke training en ook van CRT veroorzaken. Als deze mechanismen bekend zijn, kunnen er betere behandelmodaliteiten voor beide therapeutische interventies ontwikkeld worden. Ook dient er onderzoek gedaan te worden naar de vraag of en hoe zowel CRT als fysieke training kunnen worden ingezet in de preventie van hartfalen (helaas kan hartfalen niet meer genezen worden wanneer het zich eenmaal ontwikkeld heeft). Wat betreft CRT is de 'vroege' toepassing in zekere zin een dilemma (qua risico en kosten), maar voor fysieke training is dit niet zo (geregelde lichamelijke inspanning wordt aanbevolen als primaire preventie van hart- en vaatziekten). Het is de vraag of fysieke training in populaties met een verhoogd risico op hartfalen, zoals patiënten met een myocardinfarct in de voorgeschiedenis, niet als standaardtherapie, naast de standaard farmacologische behandeling, ingezet moet worden om het ontstaan van hartfalen te voorkomen of althans uit te stellen.

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LIST OF FREQUENTLY USED ABBREVIATIONS

$\Delta\dot{v}o_2/\Delta w$, oxygen uptake-work rate relation
A-II, angiotensin II
ANP, atrial natriuretic peptide
AVP, arginine-vasopressin
BNP, brain natriuretic peptide
BP, blood pressure
BPV, blood pressure variability
BRS, baroreflex sensitivity
CHF, chronic heart failure
CI, confidence interval
CRT, cardiac resynchronization therapy
CSAR, cardiac sympathetic afferent reflex
GABA, gamma-aminobutyric acid
HF, heart failure
HR, heart rate
HRV, heart rate variability
IBI, inter beat interval
LF, low frequency
LVEF, left venticular ejection fraction
LVEDV, left ventricular end diastolic volume
LVESV, left ventricular end systolic volume
MLWHFQ, Minnesota Living with Heart Failure Questionnaire
MSNA, muscle sympathetic nerve activity
NTS, nucleus tractus solitarii
NYHA, New York Heart Association classification
OUES, oxygen uptake efficiency slope
RAAS, renin-angiotensin-aldosteron-system
ROC, receiving-operating characteristic
RVLM, rostro ventrolateral medulla
SBP, systolic blood pressure
SDNN, standard deviation of the intervals between normal heart beats
TF, transfer function
VAT, ventilatory anaerobic threshold
$\dot{v}co_2$, carbon dioxide output
$\dot{v}e$, minute ventilation
$\dot{v}o_2$ kinetics, oxygen uptake kinetics
$\dot{v}o_{2\,max}$, maximal oxygen uptake
$\dot{v}o_{2\,peak}$, peak oxygen uptake
w_{max}, maximal workload

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Biventricular pacing-induced acute response in baroreflex sensitivity has predictive value for mid-term response to cardiac resynchronization therapy.
Submitted

SCIENTIFIC AWARDS

First prize in recognition of best oral presentation in the session electrophysiology / arrhythmias, annual autumn meeting Netherlands Society of Cardiology,
The Netherlands, October 2007.

First prize in recognition of best poster presentation, 14th Leiden Vascular Medicine Scientific Day,
The Netherlands, November 2007.

NAWOORD

Ruim 4 jaar geleden begon ik aan mijn promotietraject. Mijn grote passie was op dat moment polsstokhoogspringen. Helaas heb ik door een aanhoudende blessure het polsstokhoogspringen niet door kunnen zetten. Ik heb echter ondervonden dat het komen tot een proefschrift veel overeenkomsten heeft met het komen tot de ultieme sprong bij het polsstokhoogspringen. Zo moeten er voor beiden aan een aantal vereisten voldaan zijn.

Een goede sprong valt of staat met de juiste techniek. Om deze techniek zo goed en zo snel mogelijk aan te leren is het van groot belang om een goede polsstokcoach te hebben die op de juiste momenten de juiste aanwijzingen geeft. Dit is bij het maken van een proefschrift niet anders. Gelukkig heb ik de afgelopen vier jaar samen kunnen werken met een bevlogen coach. Deze coach had altijd aanwijzingen, zat nooit om woorden verlegen en ik kon altijd bij hem terecht. Bedankt voor de prettige samenwerking!

Hoewel de polsstokcoach de meest bepalende coach is, kan een goede springer het niet af met enkel een polsstokcoach. Een goede springer moet namelijk ook technisch goed kunnen lopen en een acrobatisch vermogen bezitten. Gedurende de afgelopen vier jaar heb ik naast een directe coach, ook nog twee andere coaches gehad. Beiden hebben, ieder op hun eigen manier, mij de afgelopen jaren voorzien van prikkelend commentaar. Daarnaast hebben ze, op voor mij zeer belangrijke momenten, deuren geopend die anders niet zo snel open waren gegaan. Bedankt!

Naast coaches die voornamelijk op het technische vlak de springer ondersteunen, is het prettig om ook een soort mentale coach te hebben. Aangezien in mijn geval deze mentale coach direct gekoppeld was aan de inclusie van de deelnemers voor mijn studie en deze inclusie ver achterliep bij wat we gehoopt hadden, was ik niet altijd vrolijk en positief gestemd als ik hem zag. Toch wist hij altijd wel een glimlach op mijn gezicht te toveren en was hij er een kei in om mij alles van een zonnigere kant te laten zien. Ik wil hem dan ook graag bedanken voor zijn nooit aflatende goede humeur, maar ook voor zijn inzet voor mijn studie.

Een goede medische begeleiding is voor een springer zeker ook een vereiste. Als sporter heb ik altijd de luxe gehad om door gedreven en capabele fysiotherapeuten begeleid en opgelapt te worden. Om als promovenda niet in blessures te verstranden heb je ook een goed 'medisch' team nodig dat je onderzoek op de rails houdt. In mijn geval was er een enorm 'medisch' team dat mijn onderzoek draaiende heeft gehouden. Datamanagers, verpleegkundigen, research assistentes, medewerkers van de planning, fietslaboranten, medewerkers van de ECG dienst, analisten, cardiologen, revalidatieartsen, fysiotherapeuten, trainers, secretaresses, teammanagers, en medewerkers van de computerondersteuning, een ieder heeft zo zijn eigen aandeel in het onderzoek gehad en zonder jullie was dit proefschrift zeker in onoverkomelijke blessures vastgelopen. Ik wil jullie dan ook hartelijk bedanken voor jullie inzet en enthousiasme.

Met goede coaches en een medisch team ben je er echter nog niet, trainingsmaatjes zijn ook erg belangrijk. Trainingsmaatjes werken immers motiverend, je kunt veel van ze leren, er enorm veel lol mee hebben en als je geluk hebt houd je er een mooie vriendschap aan over. De afgelopen 4 jaar heb ik mijn trainingsmaatjes gevonden in mijn 'tuin' collega's!

Nu zou je denken we zijn er bijna, we hebben immers een aantal coaches, een medisch begeleidingsteam en trainingsmaatjes. Niets is echter minder waar. Voor de ultieme sprong heeft een polsstokhoogspringer immers een polsstok nodig. Je moet dus goed materiaal hebben! Dit is bij het doen van onderzoek niet anders. Zonder de inzet van vele patiënten die het mij mogelijk gemaakt hebben om gebruik te maken van het door hen verschafte onderzoeksmateriaal was dit onderzoek simpelweg niet mogelijk geweest. Allen wil ik bedanken voor hun deelname aan mijn onderzoek, hun mooie verhalen en het in mij gestelde vertrouwen.

Ook het publiek heeft een inspirerende rol, met het publiek achter je kan je immers de hele wereld aan. Hoewel het publiek vaak niet weet wat je bezield om met een stok over een lat te willen springen, staan ze daar toch maar. Ditzelfde geldt voor het promotietraject, probeer namelijk maar eens aan je familie en vrienden uit te leggen waarom je in hemelsnaam vier jaar lang op een onderwerp aan het studeren bent en daarbij mensen onder stroom zet… Ondanks dat, waren mijn vrienden en familie er altijd! Lief publiek, ik wil jullie dan ook bedanken voor jullie onvoorwaardelijke aanwezigheid. Zonder jullie zou mijn wereld een stuk minder mooi zijn.

Om nu werkelijk tot de ultieme sprong of een proefschrift te komen zijn er naast alle tot nu toe genoemde voorwaarden nog twee zeer belangrijke vereisten te noemen. Het is alom bekend dat het echte trainingseffect niet tijdens de training maar in de daarop volgende rust bereikt wordt. Na al dat trainen/werken voor die ultieme prestatie is het dus van groot belang om een fijn thuis te hebben. Dat thuis vind ik bij mijn vriend. Iedereen die hem voor het eerst ziet heeft als opmerking: 'Wat is hij groot.' In mijn ogen is hij echter niet alleen groot maar zeker ook groots!

Als laatste vereiste heeft iedere sporter/promovenda een beschermengel nodig. Mijn dappere kleine mannetje, als ik naar de wolken kijk zie ik jou.

CURRICULUM VITAE

The author of this thesis was born on 6 March 1979 in Utrecht the Netherlands. In 1997 she graduated and received her Gymnasium diploma from the 'Openbare Scholengemeenschap Schoonoord' in Zeist. In the same year she started her study Human Movement Sciences at the Vrije University in Amsterdam. In 2005 she graduated with a major field in sports. Her main research project was conducted at the School of Sport and Exercise Science, University of Sydney Australia. After graduation, she worked as a sports coach at the Pim Mulier organization and as a counselor food and exercise for the alife@work project at the EMGO institute in Amsterdam. In 2005 she started working as a PhD student at the department of Cardiology of the Leiden University Medical Center. Under supervision of Dr. Ir. C.A. Swenne, Prof. Dr. E.E. van der Wall and Prof. Dr. M.J. Schalij she investigated the effects of exercise training and of biventricular pacing on fitness in chronic heart failure patients.

De auteur van dit proefschrift is geboren op 6 maart 1979 te Utrecht. Zij behaalde haar gymnasiumdiploma in 1997 aan de Openbare Scholengemeenschap Schoonoord te Zeist. In datzelfde jaar begon ze aan de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. In 2002 behaalde ze haar doctoraal examen met als afstudeerrichting Sport. In het kader van het doctoraal examen werd een onderzoeksstage uitgevoerd bij School of Exercise and Sport Science, University of Sydney, Australië. Na haar studie werkte zij als sportdocent bij de Pim Mulier organisatie en als counselor voeding en beweging voor het alife@work project aan het instituut voor Extramuraal Geneeskundig Onderzoek te Amsterdam. Zij startte in 2005 met haar promotieonderzoek onder leiding van dr. ir. C.A. Swenne aan de afdeling Hartziekten van het Leids Universitair Medisch Centrum (promotores prof. dr. E.E. van der Wall en prof dr. M.J. Schalij). De resultaten van haar promotieonderzoek staan beschreven in dit proefschrift.