Peter R. Wright

Clinical effects of specific exercise interventions in CHF and COPD patients

TECHNISCHE UNIVERSITÄT
CHEMNITZ

Faculty of Behavioural and Social Sciences · www.tu-chemnitz.de/hsw

Peter Wright

Clinical effects of specific exercise interventions in CHF and COPD patients

Peter Wright

Clinical effects of specific exercise interventions in CHF and COPD patients

TECHNISCHE UNIVERSITÄT
CHEMNITZ

Universitätsverlag Chemnitz

2013

Imprint

Bibliographic Information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie (German National Bibliography); detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

This dissertation is submitted to the Faculty of Behavioural and Social Sciences of the Technische Universität Chemnitz.

Day of submission: 10 June, 2013

Supervisor: Prof. Dr. (MD) Henry Schulz
(Technische Universität Chemnitz)

First Assessor: Prof. Dr. (MD) Henry Schulz
(Technische Universität Chemnitz)

Second Assessor: Prof. Dr. Günter Tidow
(Humboldt-Universität zu Berlin)

Day of oral examination: 30 July, 2013

Technische Universität Chemnitz/Universitätsbibliothek
Universitätsverlag Chemnitz
09107 Chemnitz
GERMANY
http://www.bibliothek.tu-chemnitz.de/UniVerlag/

Production and Distribution
Verlagshaus Monsenstein und Vannerdat OHG
Am Hawerkamp 31
48155 Münster
GERMANY
http://www.mv-verlag.de

ISBN 978-3-941003-92-7

URL: http://nbn-resolving.de/urn:nbn:de:bsz:ch1-qucosa-122066

LIST OF CONTENT

i. List of Abbreviations

%	Percentage
£	Pound
12RM	12-Repetition-Maximum
6MWT	6-Minute-Walk-Test
α1 Antitrypsin	a glycoprotein which protects tissues from enzymes of inflammatory cells.
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACC	American College of Cardiology
ACPICR	Association of Chartered Physiotherapists Interested in Cardiac Rehab.
ACSM	American College of Sports Medicine
ADL	Activities of daily living
AHA	American Heart Association
ANOVA	One factorial variance analysis
ARB	Angiotensin receptor blocker
ATS	American Thoracic Society
bpm	Beats per minute
BHF	British Heart Foundation
BMI	Body-Mass-Index
BMR	Basal Metabolic Rate
BNP	Brain Natriuretic Peptide
BODY	Bodyplethysmography
BTS	British Thoracic Society
Ca	Chemical symbol for calcium.
ca.	Circa
CABG	Coronary bypass procedure
CG	Control Group

CHD	Coronary heart disease
CHF	Chronic/Congestive Heart Failure
CI	Confidence interval
cm	Centimeter
CMP	Cardiomyopathy
COPD	Chronic Obstructive Pulmonary Disease
CPG	Comparison Group
CRQ	Chronic respiratory questionnaire
CRT	Cardiac resynchronisation therapy
CTG	Circuit Training Group
CVD	Chronic Vascular Disease
DALY	Disability-Adjusted Life-Year
DCM	Dilative Cardiomyopathy
DGPR	Deutsche Gesellschaft für Prävention und Rehabilitation
DVGS	Deutsche Vereinigung für Sporttherapie und Gesundheitssport
e.g.	For example
ECG	Electrocardiography
EF	Ejection Fraction of the heart
ESC	European Society of Cardiology
ETG	Endurance Training Group
et al.	et alii
etc.	et cetera
FEV_1	Forced expiratory volume in 1 second
FEV_1/ FVC	Tiffeneau-Index
FVC	Forced vital capacity
FVCin	Forced inspiratory vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HF	Heart Failure
HRQL	Health related quality of life
i.e.	For example

IDDM	Insulin dependent diabetes mellitus.
IG	Intervention Group
IGF	Insulin like growth factor
IMT	Inspiratory Muscle Training
IMTG	Inspiratory Muscle Training Group
K	Chemical symbol for potassium
Kg	Kilogram
L	Litre
LTOT	Long term oxygen therapy
LVEDD	Left ventricular end-diastolic diameter
m	Metre
M.	Musculus
max	Maximum
mb	Millibar
MD	Mean difference
METS	Metabolic equivalent
mg/dL	Milligram per decilitre
MHFQ	Minnesota Living with Heart Failure Questionnaire
MI	Myocardial infarction
min	Minimum
min	Minute
ml	Millilitre
mmHg	Millimeter hydrargyrum
mmol/L	Millimol per Litre
MV	Mean value
n	Number
n.s.	Not significant
Na	Chemical symbol for sodium.
NTG	Non-training group (comparison group)
NIDDM	Non-insulin dependent diabetes mellitus.

NT-pro-BNP	N-Terminal Pro-hormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
p	Error probability
PaO_2	Partial pressure of oxygen
pCO_2	Partial pressure of carbon dioxide.
pg/mL	Pictograms per millilitre
pH	Measure of acidity/alkalinity of a liquid
Plmax	Maximal inspiratory pressure
pO_2	partial pressure of oxygen
Qc	Cardiac output
Qol	Quality of life
RCT	Randomised controlled trial
RM	Repetition Maximum
RPE	Received Perception of Exertion
RPP	Rate-Pressure-Product
RQ	Respiratory quotient
s	Second
SaO_2	Oxygen saturation
SD	Standard deviation
SF-36	Short-Form Health Survey
SGRQ	St George's respiratory questionnaire
STG	Strength Training Group
SV	Stroke volume
ß	Beta
U.S.A.	United States of America
UK	United Kingdom
VO_2	Oxygen uptake
VO_{2peak}	Peak oxygen uptake
W	Watt
WHO	World Health Organisation

ii. List of Figures

iii. List of Tables

1 INTRODUCTION

All modern industrialised countries are facing similar problems. An increasingly mechanised environment, as well as changing demographic, social and economic conditions are challenging western societies nowadays. Especially the increase of prevalent conditions such as obesity, diabetes mellitus, respiratory and cardiac diseases lead to exploding costs in health care systems. This is primarily caused by expensive medication, hospitalisation and lost work days due to illness. Some of the most costly conditions are chronic heart failure (CHF) which has a high prevalence especially in the older population and may affect as much as 10% of this cohort (U.S.A.) [1], and chronic obstructive pulmonary disease (COPD) which has shown one of the most dramatic increases in mortality in the developed world over the past 40 years - from 16 deaths/100.000 population in 1963 in the U.S. to 42 in 2010 which equates to an increase of 156% over this period [2]. It is therefore a leading cause of morbidity and mortality worldwide and should be considered as a major economic and social burden that is both substantial and increasing [3].

In both conditions, exercise therapy should play an integral part in maintaining the patient's maximal level of independence and functioning, as well as slowing or possibly even stopping the progression of the condition, in a downward spiral, with increasing symptoms and loss of functional capacity. This in return might be reflected in reduced health care costs. In this context the main objectives for these doctoral theses are:

a. Proving the safety of different exercise modalities.
b. Identifying the most effective exercise interventions in regards to clinical parameters.
c. Proving the feasibility of outpatient rehabilitation programmes for two high risk populations – CHF and COPD patients.

This work, therefore, combines three studies looking into the effects of non-pharmaceutical interventions – predominantly different exercise regimes in the two major conditions in the mortality statistics – chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). The reason for combining these two conditions not only lies in the epidemiological relevance, but also in their disease specific symptoms which are very similar on the musculoskeletal and hormonal level, not to mention the subjective symptoms of exercise intolerance and shortness of breath. Another reason for dealing with these two internal diseases jointly, in an exercise/rehabilitation context is the fact that both groups are considered to be high risk patients – especially as CHF and COPD are classed

as so called “end-stage conditions” with a very poor prognosis. As such these patients should benefit greatly from structured exercise interventions which theoretically should be quite similar, if not the same for both conditions. Thus the presented studies incorporate both conditions with the title: *Clinical effects of specific exercise interventions in CHF and COPD patients.*

CHF

According to the European Society of Cardiology chronic heart failure (CHF) - also known as congestive heart failure has a prevalence of 0.4 to 2% in the overall population [4] and up to 14.7% in men over 80 years in the U.S. [1]. The variation of this figure is country specific and also depends on the findings in different studies. However, this only represents the peak of the iceberg and many CHF patients – especially with a mild form of CHF remain undiagnosed. The current development in Europe shows an increasing number of CHF patients with approx. 300.000 new cases every year and annual hospitalisation rates of approx. 240.000 in most countries [5]. CHF is the most common reason for hospitalisation in over 65 year olds and therefore has a very high health-economic relevance.

Heart failure is a complex of symptoms that are related to the inadequate perfusion of tissue during exertion and often to the retention of fluid. The non-cardiac factors such as neurohormonal changes, muscle atrophy and others, independently can cause dyspnoea, fatigue, and oedema that are characteristic of the clinical syndrome of CHF [6,7]. The treatment of heart failure therefore involves counteracting two related but largely independent processes.

A key role in this context plays the so called vicious cycle of heart failure, which is mainly characterised by an increase of symptoms during physical activity, therefore the patient avoids exercise and this initiates de-conditioning processes which lead to a further loss of functional capacity on all levels, including skeletal muscle mass, catabolic hormonal changes and an increase of cardiac specific symptoms [8,9,10,11].

Traditionally patients have been recommended to avoid physical exercise, because it was believed that the strain might aggravate the cardiac condition and is therefore harmful. This belief has been challenged in the last two decades and several studies proved the positive effects of exercise training in CHF patients [12,13,14,15,16,17]. Most studies used an endurance training intervention; few investigated the effects of strength training exercises [18,19,20].

COPD

Chronic obstructive pulmonary disease (COPD) is defined by the WHO as a lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. Historically such terms as “chronic bronchitis” and “emphysema” were used to describe aspects of the condition, but these are now included within the COPD diagnosis. Chronic asthma also used to be included under the umbrella term of COPD although in more recent years its inclusion has become more debatable. The consensus and global medical opinion is now moving away from separate disease classifications and has moved to the one, more encompassing diagnostic term of COPD.

210 million people are estimated to have chronic obstructive pulmonary disease (COPD) worldwide [21]. Smoking is considered to be the main cause for COPD. COPD is estimated to produce health care costs of 5.471 billion € [22]. However, these are only direct costs referring to diagnosed COPD patients which means that a great number of COPD patients remain undiagnosed, but produce health care costs nevertheless – for example in the UK an estimated 3 million people have COPD of which only 900,000 have been diagnosed [23]. Presently there are no valid figures published for the prevalence of COPD in Germany. However, the prevalence of chronic bronchitis in the adult German population is estimated to be 10-15% [24].

The significance of COPD in the health-economic context and for the individual patient stands in contrast to the lack of patient-centred care in many areas of which exercise therapy/rehab should be a key one. Physical training not only contributes to a general stabilisation of the constitution of COPD patients, but also leads to an improvement of the immune situation and pulmonary function. The health and conditional decline of COPD patients is also caused by a vicious cycle similar to CHF, consisting of illness-related inactivity and the progressive worsening of symptoms. The goal of every exercise therapy should be therefore to end this vicious cycle. In principle, numerous forms of exercise show a positive effect on the progression of the disease. However, effectiveness and efficiency of individual measures can vary. The toleration of different exercise regimes for COPD patients [25] behave likewise.

Common Symptoms – Common (Exercise) Therapy

CHF and COPD are two separate conditions – one relating to a disease of the respiratory system, the other to the heart. These conditions can occur in conjunction in the form of a right ventricular CHF caused by pulmonary

hypertension which in itself can be caused by COPD. But this is not the only link between the two conditions – as elaborated above the symptoms of CHF and COPD are also very similar. In this context the catabolic processes in both are in the focus of interest as well as the very similar subjective symptoms of the patients which present themselves predominantly as shortness of breath and a significant increase of symptoms during exercise and even restrictions in activities of daily living.

In CHF cardiac factors, such as ventricular dysfunction, contribute to the same vicious cycle consisting of the progressive process of cardiac remodelling as the non-cardiac factors which are characteristic of the clinical syndrome of heart failure [8,9]. This is very similar in COPD with a chain of catabolic effects caused by inflammatory processes, hypoxia and disuse. Focusing on these effects, much of the new research into treating cardiac and pulmonary disease is looking into targeting the systemic problems.

There are still a few gaps in the understanding of the mechanisms underlying the muscle wasting of patients with COPD. However, it is possible to identify a range of systemic factors which are known to be abnormal in many COPD patients, and are likely to have an impact on muscle protein metabolism which lead to a significant loss of muscle tissue, especially in the fatigue resistance slow twitch type 1 fibres [26,27]. Parallel to this loss in type I fibres, a significant increase of type IIX fibres was found in COPD patients [28] and of type 2A fibres in CHF patients respectively [29]. According to JAGOE and ENGELEN [30] the extracellular factors likely to be involved in muscle wasting in COPD are: reduced testosterone, reduced IGF-1, insulin resistance, chronic hypoxemia, steroid treatment, reduced or altered contractile activity, negative energy balance, acidosis and increased pro-inflammatory cytokines.

In CHF the failure to provide peripheral tissues with sufficient amounts of oxygen is accompanied by similar maladaptive responses as in COPD that include pathophysiological pathways that may lead to an anabolic-catabolic imbalance with the development of cardiac cachexia. The deficiencies or resistance to growth hormone and testosterone also plays an important role in the pathophysiology of CHF. The role of appetite regulation in the context of a negative energy balance [31] is similar as in the COPD population. Systemic inflammation too is associated with cardiovascular disease, especially the end stages of heart failure [32]. The enhanced catabolic status is therefore significantly associated with exercise intolerance, ventilatory inefficiency, and chronotropic incompetence in CHF patients, suggesting a significant contributing mechanism to

their limited functional status [33]. These circumstances drive the catabolic processes of muscle, bone, and fat wasting in CHF patients.

Due to the common systemic symptoms in CHF and COPD, as elaborated above - especially muscle wasting as it is associated with impaired skeletal muscle function, worse quality of life and poorer prognosis; a symptom specific intervention should be applied to treat these two conditions adequately. Both conditions are so similar from a rehabilitation/sports medicine point of view that it seems a logical consequence to investigate specific exercise interventions for CHF and COPD in conjunction and also to develop rehabilitation structures where both patient groups can be treated together in an exercise setting.

In this context, resistance and/or strength training should be especially considered as it seems to meet the demands of these conditions perfectly because of its symptom-specific anabolic effects (low testosterone and IGF1 levels) and a better toleration by the patients because of the intermittent nature of the exercise which can prevent or at least reduce dyspnea and general discomfort during the exercise therapy and thereby increase the compliance of patients to exercise.

Hence, this work presents three studies in the area of cardiac and pulmonary rehabilitation of which the first compared different exercise regimes in CHF patients. The aim of this study was to examine the different effects of an endurance training using the continuous training principle, a high intensity strength training and a circuit training vs. a dietary comparison group (non-exercising group) and control group in an outpatient setting on cardiac specific parameters such as ejection fraction (EF), left ventricular end diastolic diameter (LVEDD), NYHA classification and NT-pro-BNP as well as exercise specific parameters using peak oxygen consumption (VO_{2peak}), strength and also hospitalisation rate. The other two studies were conducted in a COPD rehabilitation setting: the first COPD study investigated the effects of a 12-week outpatient high intensity strength training programme on pulmonary specific parameters, such as COPD classification, FEV_1, testosterone levels, medication consumption and exacerbation as well as exercise performance in the form of endurance, strength and flexibility. Additionally the health related quality of life (HRQL) was measured as well as the depression profile of this population. The second COPD study examined the effects of a conventional exercise therapy vs. exercise therapy plus inspiratory muscle training (add on therapy) in a clinical setting on the same pulmonary parameters as well as HRQL, inspiratory muscle

strength, activities of daily living performance and also exercise specific parameters.

The gained knowledge could aid in the process of setting up specific exercise referral/rehabilitation programmes phase 3 (4 in the UK) for CHF and COPD patients who still do not have sufficient access to structured exercise. This work will also increase the knowledge base on specific interventions which are safe and disease specific in their effects as well as other add on therapies in order to maximise the therapy benefit for this population.

2 LITERATURE ANALYSIS CHF AND COPD

2.1 Clinical Aspects

2.1.1 CHF

DEFINITION AND PREVALENCE

Chronic heart failure (CHF) is a condition characterised by a reduction in cardiac output that is often insufficient to meet the demands of vital organs and physiological systems. The aetiology of heart failure is caused by the impaired ability of the heart to either pump or accept blood [34, p. 151].

Chronic heart failure is also recognised as congestive heart failure which is more commonly used in North America than Europe. CHF is differentiated into two types – systolic heart failure (left ventricular dysfunction) and diastolic heart failure (right ventricular dysfunction). The pathogenesis of both conditions is quite different, although the effects and symptoms are very similar. Systolic heart failure has a significantly higher prevalence and therefore stands in the focus of epidemiological studies, rather than diastolic heart failure which is usually a secondary disease of COPD.

In the developed countries, cardiovascular diseases are the most frequent causes of death in the population. According to the German Federal Office of Statistics, more than 200.000 patients die of chronic ischaemic heart disease, acute myocardial infarction and chronic heart failure in Germany each year. Apart from the severity of CHF, its prevalence is of significant importance. Per one thousand inhabitants, between 5 and 65 new cases of the disease are diagnosed depending on the age groups each year. In total, about 400.000 people are living with diagnosed chronic heart failure in Germany [35]. This figure is constantly growing.

The overall incidence and prevalence figures reported in the medical literature vary widely, mainly because different sets of diagnostic criteria have been used. Although reliable estimates are lacking in many countries, the prevalence of heart failure is estimated as 2%-3% of the adult
population and increases with age. Over 26 million people suffer from heart failure around the world and over 3.5 million people are newly diagnosed with heart failure every year in Europe alone. The long-term prognosis associated with heart failure is worse than that associated with the majority of cancers, with 50% mortality after 4 years [36].

The prevalence of CHF may be even higher in Europe. Although significant differences have been noted between studies in different countries and age groups in general, ranging from as low as 2.8% to as high as 16.1% – see table 1.

Table 1: CHF in different community populations (adapted from Rodeheffer RJ, 2003) [37].

Study	Sample size (age range, y)	EF method	LVD EF definition	Prevalence, %		
				VE	M-mode	2D
Gardin *et al.*	5201	VE	Abnormal EF by VE	3.7	-	-
CHS	(65-100)					
McDonagh *et al.*	1467	2D	2 SD < nl mean; < 35%	-	-	7.7
Glasgow	(25-75)					
Bröckel *et al.*	1566	M-mode	2 SD < nl mean; < 48%	-	2.8	-
Regensburg	(25-75)					
Mosterd *et al.*	2267	M-mode	EF < 42.5%	-	3.7	-
Rotterdam Study	(55-94)					
Redfield *et al.*	2036	M-, 2D , VE	2 SD < nl mean; < 50%	6.0	4.2	4.8
Olmsted County PAVD	(45-96)					
Devereux *et al.*	1066	M-mode	2 SD < nl mean; < 54%	-	16.1	-
Strong Heart Study	(49-78)					
Davies *et al.*	6286	2D	EF < 50%	-	-	5.3
West Midlands, UK	(45+)					

2D--two-dimensional Simpson method; CHS--Cardiovascular Health Study; EF--ejection fraction; LVD--left ventricular dysfunction; nl--normal; PAVD--prevalence of asymptomatic ventricular dysfunction; SD--standard deviation; VE--visual estimate.

One of the main causes for heart failure is coronary heart disease (CHD). Mortality from CHD is falling rapidly, whilst morbidity from CHD and other heart diseases appears to be rising, especially in older age groups. In those aged 65 and older, morbidity has risen by around one third since the late 1980's. In the UK for instance around 1.3 million people have had a heart attack and approximately 2 million people are suffering from Angina, the most common form of CHD. Around 670.000 people have been diagnosed (and a further 230.000 probable) with heart failure [38].

Recent statistics on the incidence and prevalence of CHF in the U.S. indicate that over five million Americans are affected by heart failure, with over 550.000 new

cases diagnosed each year. Additionally, more than 999.000 hospitalisations each year caused by CHF produce costs in excess of $24 billion [39].

PATHOGENESIS

The most frequent cause is coronary heart disease with a past myocardial infarction. Due to the formation of scars in the myocardium, the pumping performance is reduced resulting in an ischaemic cardiomyopathy. Further causes are "valvular diseases" in terminal state and the so-called dilative cardiomyopathy. Comparing the survival rates of CHF with the survival rates of cancer, myocardial insufficiency seems to have markedly worse survival prospects. Only lung cancer has even worse prospects.

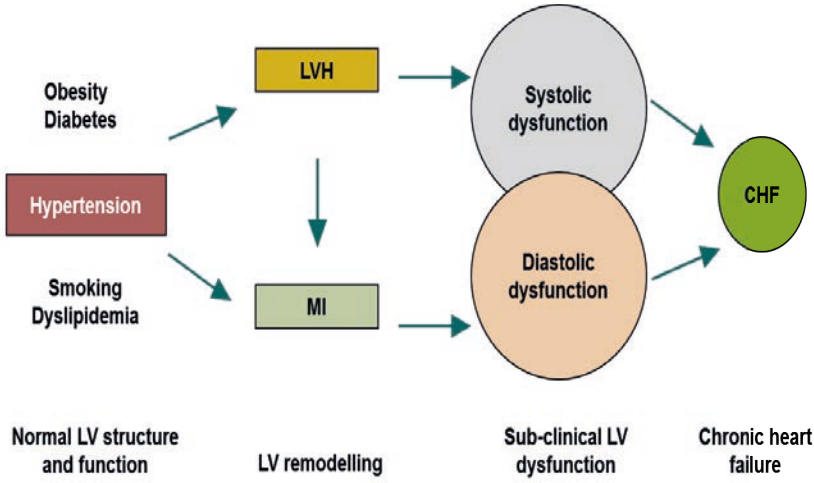

Figure 1: Progression from hypertension to CHF (adapted from Vasan RS, Levy D 1996) [40].

In summary conditions that could lead to heart failure include: coronary heart disease, hypertension, myocardial infarction, diabetes mellitus, cardiomyopathy, heart valve disease (e.g. valvular stenosis or valvular regurgitation), infection in the heart valves or of the heart muscle (myocarditis), congenital heart disease, severe lung disease (COPD, pulmonary hypertension also caused by other pulmonary conditions) or obstructive sleep apnoea – in some cases even pericarditis.

PATHOPHYSIOLOGY AND SYMPTOMS

Chronic heart failure involves two related but largely independent processes. Left ventricular dysfunction (systolic heart failure), regardless of cause (coronary artery disease, cardiomyopathy, hypertension, or valvular disease), develops through ventricular remodelling which results in a dilated chamber with a low ejection fraction, leading to episodes of arrhythmia, progressive pump failure, and premature death. Right ventricular dysfunction (diastolic heart failure) develops similar to systolic heart failure, but the cause is usually pulmonary hypertension and/or a history of COPD. Diastolic heart failure, however, is less prevalent than systolic heart failure. In both types of CHF non-cardiac factors (neurohormonal stimulation, endothelial dysfunction, vasoconstriction, and renal sodium retention) may or may not be stimulated by ventricular dysfunction, but ultimately contribute to the same progressive process of cardiac remodelling; the non-cardiac factors independently cause the dyspnoea, fatigue, and oedema that are characteristic of the clinical syndrome of CHF.

The symptoms of heart failure are predominantly those of congestion, caused by an elevated ventricular filling pressure, and of fatigue and organ-system dysfunction, related to inadequate cardiac output in response to stress. Vascular and neuroendocrine mechanisms are important contributors to the abnormalities in regional blood flow, renal retention of sodium, and pulmonary congestion that lead to symptoms. Activation of the renin-angiotensin system and the sympathetic nervous system may also contribute to the structural changes in the heart and peripheral vasculature that mediate the progressive remodelling of the left ventricle [41]. The inadequate delivery of blood to specific areas may be associated with a variety of physiological sequelae in the progression of CHF, as shown in table 2.

Table 2: Physiological consequences of chronic heart failure (adapted from AACVPR: Guidelines for cardiac rehabilitation and secondary prevention programs, 2004; p. 153) [34].

Pathology	Effects
Cardiovascular	Decreased myocardial performance, with subsequent peripheral vascular constriction to increase venous return (attempting to increase stroke volume and cardiac output).
Pulmonary	Pulmonary oedema because of elevated cardiac filling pressures, resulting from poor cardiac performance and fluid overload.
Renal	Water retention resulting from decreased cardiac output.
Neurohormonal	Increased sympathetic stimulation that eventually desensitises the heart to beta-1 adrenergic receptor stimulation thus decreasing the heart's inotropic effect.
Musculoskeletal	Skeletal muscle wasting and possible skeletal muscle myopathies as well as osteoporosis resulting from inactivity or other accompanying disease.
Hematologic	Possible polycythaemia, anaemia, and haemostatic abnormalities resulting from a reduction in oxygen transport, accompanying liver disease, or stagnant blood flow in the heart's chambers resulting from poor cardiac contraction.
Hepatic	Possible cardiac cirrhosis from hypo-perfusion resulting from inadequate cardiac output or hepatic venous congestion.
Pancreatic	Possible impaired insulin secretion and glucose tolerance as well as the source of a possible myocardial depressant factor.
Nutritional/ biochemical	Anorexia that leads to malnutrition (protein-calorie and vitamin deficiencies) and cachexia.

It is apparent from this table that a CHF patient suffers from a syndrome in which pathophysiological and compensatory mechanisms act on the body in an attempt to maintain an adequate ejection of blood from the heart. However, these mechanisms may improve or maintain for only a temporary period, after which heart failure will likely progress in a downwards spiral [34]. The clinical manifestations of CHF are: dyspnoea and fatigue, tachypnea, orthopnoea, peripheral oedema, cold, pale and possibly cyanotic extremities, weight gain,

hepatomegaly, jugular venous distension, tubular breath sounds and consolidation, sinus tachycardia and rarely presence of a third heart sound [42]. The most relevant objective parameter to identify heart failure is a hypertrophic heart in conjunction with an inadequately low ejection fraction (EF).

Identification of the signs and symptoms of heart failure provide important information about the severity of CHF as well as the domain of disablement most effected by heart failure. Thus, CHF is categorised into four classes which relate to objective cardiac parameters, but also to physical limitations as shown in table 3.

Table 3: New York Heart Association-4 stage classification system of heart failure.

Illustrations	NYHA Classification & Criteria	Objective Criteria
	**I.** Heart disease without physical Limitation. Everyday physical activity does not cause inadequate exhaustion, arrhythmia, breathing difficulties or an angina pectoris.	No objective signs for a cardiovascular disease
	**II.** Patient with a clear heart condition and light physical restrictions. No complaints during rest; everyday physical activities cause moderate exhaustion, breathing difficulties and arrhythmia, breathing difficulties or angina pectoris.	Objective signs for a moderate cardiovascular disease
	**III.** Patient with heart disease and significant physical restriction. Sometimes complaints during rest; every day activities cause exhaustion, arrhythmia, breathing difficulties or angina pectoris.	Objective signs for a serious to high-degree cardiovascular condition
	**IV.** Patient with heart disease. Complaints during any physical activity and during rest, immobilisation.	Objective signs for a very severe cardiovascular disease

Although the NYHA classification is internationally more commonly used, there exists another system by the American Heart Association (AHA) and American College of Cardiology (ACC) which also distinguishes four stages, but with a different definition which is based on structure and damage to the heart muscle

whereas the NYHA system is based on symptoms and physical activity restrictions of the patients.

Table 4: AHA/ACC-4 stage classification system of heart failure [43].

AHA/ACC Classification	Criteria
Stage A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.
Stage C	Symptomatic heart failure associated with underlying structural heart disease.
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.

2.1.2 COPD

DEFINITION AND PREVALENCE

The coexistence of cardiac and pulmonary disease has risen dramatically over the past three decades. Many patients, who present themselves with a significant cardio-vascular disease (CVD) such as CHD or peripheral arterial disease, also have a significant pulmonary disease and it is often the latter that causes more limitations to the patients' exercise ability. Given the prevalence of smokers or ex-smokers and the time delay - often several decades, leading up to the development of symptoms related to smoking such as in chronic obstructive pulmonary disease (COPD), it is not surprising that many patients are diagnosed with concomitant cardiac and pulmonary disease [34, p.170]. Even in a cardiac rehabilitation setting it is important to consider the possibility of the presence of a pulmonary impairment – especially COPD as up to 20% of patients who enter a cardiac rehabilitation programme will have a significant pulmonary disease symptomatology [43].

COPD is defined by the WHO as a lung disease "… characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbation and comorbidities contribute to the overall severity in the individual patients" [44]. COPD is therefore not fully reversible.

Historically, "chronic bronchitis" and "emphysema" were used to describe aspects of the condition, but these are now included within the COPD diagnosis. Chronic asthma was also included under the umbrella term of COPD although in more recent years its inclusion has become more debatable. COPD is the end result of the disease and predominantly caused by tobacco smoking and inhaling other noxa (outdoor and indoor, i.e. workplace related fumes, open fire smoke) which lead to chronic inflammation, obstruction of the airways by copious mucus secretion causing narrowing of the airways and destruction of lung tissue (self-digestion of the lungs; loss of protein structures) or even emphysema. COPD is one of the few conditions which has seen a dramatic increase in mortality statistics in the U.S. between 1963 and 1990 by as much as 156% and between 1990 and 2010 of plus 9% [45].

Table 5: Age-Adjusted Death rates for Cardiovascular and Non-cardiovascular Diseases, U.S., 1963, 1990 and 2010 (adapted from Vital Statistics of the United States, NCHS) [45].

Cause of Death	Deaths/100.000 Population			% Change 1963-2010	% Change 1990-2010
	1963	1990	2010		
All Causes	1,346	938	747	-45	-20
Cardiovascular Diseases	805	413	236	-71	-43
Coronary Heart Disease	478	218	114	-76	-48
Stroke	174	69	39	-78	-43
Other	153	125	83	-46	-34
Non-cardiovascular Diseases	541	526	512	-5	-3
COPD and Asthma	16	39	42	156	9
Other	524	487	469	-11	-4

Approximately 210 million people are estimated to have chronic obstructive pulmonary disease worldwide [46]. However, existing COPD prevalence data show remarkable variation due to the differences in survey methods, diagnostic criteria and material as well as analytic approaches. For example some national data

indicates prevalence as low as 6% of the adult population which are based on self-reporting. This reflects the widespread under-diagnosis of COPD [44]. In this context an estimated 3 million people have COPD in the UK of which only 900,000 have been diagnosed [47]. There are also no valid figures for the prevalence of COPD in Germany presently, but the prevalence of chronic bronchitis in the adult German population is estimated to be 10-15% [48]. Although epidemiological data seems incomplete and/or partially contradictive the World Health Organisation considers COPD as one of the most important causes of death in most countries. The Global Burden of Disease Study projected that COPD , which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020 [44]. This is due to the high number of smokers or ex-smokers - considering the significant lag time before showing symptoms, the ageing of the world population and better diagnostic methods as well as awareness of COPD amongst the medical profession.

According to LINGNER et al. (2007) COPD is currently ranging on place four in the mortality statistics worldwide [49]. In Germany over six million people are affected by COPD producing total annual costs of four billion Euros and it is therefore the leading cost producer among pulmonary conditions and is the main reason for hospitalisation next to pneumonia and lung cancer [50]. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% which equates to 38.6 billion Euros. In the U.S. the direct costs of COPD are estimated to be as high as $29.5 billion with additional indirect costs of $20.4 billion [44].

These results also suggest that the average age of retirement is around 54 years. This means a high societal and economic impact in all countries, particularly where typical state retirement ages are higher such as in Germany and the UK [50]. The socio-economic effect is also depending on the severity of COPD. The more severe, the higher the financial burden of this condition. There seems to be a geographical difference in the distribution of COPD severity stages in a population – see figure 2. These differences may be caused by diagnostic methods, accessibility to health care, but also by culture and/or country specific lifestyles as well as work environment differences and occupational health standards respectively. The following diagram shows the distribution of COPD severity stages in working age people of several countries, including Germany and the UK.

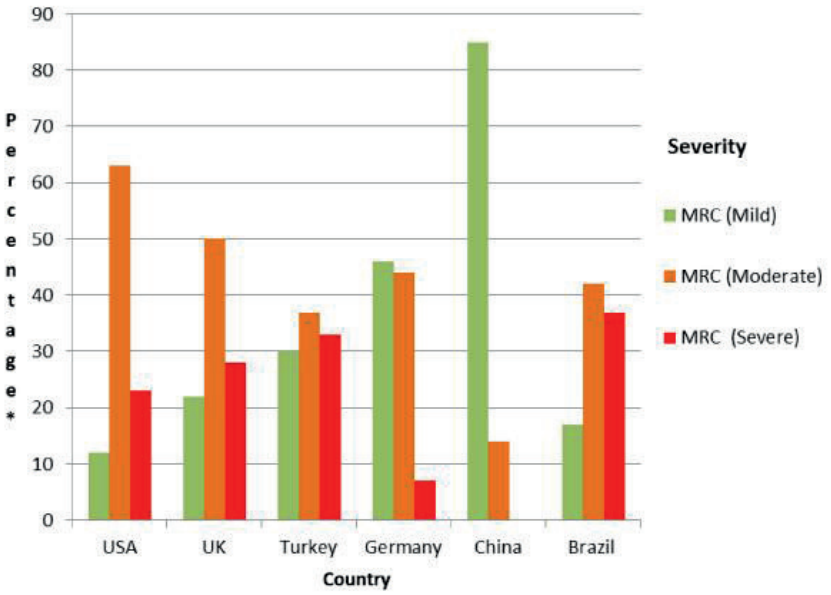

Figure 2: Severity (MRC) level analysed by country [50]. This graph presents percentage data for severity analysed by country [severity measured using the MRC dyspnoea scale]. *percentage of respondents according to severity level as measured using the Medical Research Council [MRC] dyspnoea scale. There were no respondents in China who reported severe illness (Fletcher et al., 2011).

There is a direct relationship between the severity of COPD and the cost of care, and the distribution of costs change as the disease progresses. For example, hospitalisation and ambulatory oxygen costs soar as COPD severity increases. Any estimate of direct medical expenditures for home care under-represents the true cost of home care to society as it ignores the economic value of the care provided to these patients by family members. Furthermore, these are only costs referring to diagnosed COPD patients which means that a great number of COPD patients remain undiagnosed, but produce health care costs nevertheless. Thus, the economic burden of COPD cannot be overemphasised.

PATHOGENESIS

The main cause for COPD is lifestyle related and can clearly be identified as tobacco abuse which accounts for nine out of ten patients as the pathogenesis of COPD. It is estimated that 50% of smokers develop a COPD at some point in their life [51] – although the time delay of developing symptoms is highly individual and depends on so called "packet years" smoking, other lifestyle factors and genetic pre-disposition. Another cause for COPD, besides chronic inhalation of harmful noxa, is an alpha-1 antitrypsin deficiency which is a genetic disorder and is characterised with an early onset of COPD symptoms and usually a family history of pulmonary conditions. But this deficiency only accounts for a very small number of patients and plays no significant role in the prevalence of COPD. Although there is a significant difference in the pathogenesis and the pathophysiology of COPD and asthma [52] (see table 6) – the latter can eventually lead to COPD if untreated, but not directly. A patient with severe asthma who either remains undiagnosed or shows a poor compliance to the medication scheme can develop chronic bronchitis over a longer period of time (usually decades). This could then progress in a downward spiral to chronic obstructive bronchitis and eventually to COPD without any tobacco smoking history.

Table 6: Clinical features differentiating COPD and asthma (NICE 2010) [53].

Characteristics	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common

Smoking damages lung cells, thereby releasing the enzyme trypsin which destroys the supportive alveolar matrix. This breakdown creates redundant air sacs incapable of gaseous exchange. The remnant alveolar sacs form larger sacs or bubbles in which the lung secretions pool, provide a perfect medium for infection to proliferate and worsen the situation. This process eventually results in

emphysema. As elaborated above, a variety of other factors including environmental pollutants, cystic fibrosis and asthma may also cause or contribute to chronic airway obstruction. As the disease process continues to advance medication may become less effective at managing the symptoms of the condition as the obstructive disease process becomes irreversible.

Inevitably, this results in a progressive deterioration of pulmonary function which is reflected in a parameter called *Forced Expiratory Volume in 1 Second* or FEV_1. This is one of the key parameters to diagnose COPD which is applied in the following classification system. The stages are differentiated from 0 to 4 whereby 0 is referred to as "Risk" and 4 as severe COPD. However, there is also another terminology being used synonymously for stages 1 to 4 which are also known as GOLD 1, 2, 3, 4. The applied criteria to these stages are nevertheless the same.

Table 7: Classification of COPD severity based on post-bronchodilator FEV^1 (GOLD, 2010) [46].

Classification of COPD Severity	
Stage 0: Risk	Normal FEV_1 + symptoms (productive cough)
Stage I: Mild (GOLD 1)	$FEV_1 \geq 80\%$ predicted + chronic symptoms (productive cough, dyspnoea during exercise) $FEV_1/FVC < 70\%$
Stage II: Moderate (GOLD 2)	$50\% \leq FEV_1 < 80\%$ predicted + chronic symptoms (productive cough, dyspnoea) FEV1/FVC < 70%
Stage III: Severe (GOLD 3)	$30\% \leq FEV_1 < 50\%$ predicted + chronic symptoms (productive cough, dyspnoea) $FEV_1/FVC < 70\%$
Stage IV: Very Severe (GOLD 4)	$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure or symptoms of right ventricular heart failure $FEV_1/FVC < 0.70$

There is also another categorisation of COPD patients which predominantly refers to the severity of symptoms and risk of exacerbations and only considers FEV_1 as a

secondary criteria. This system is usually applied as a guidance for medication schemes and divides COPD patients again into four groups – group A, B, C and D. These groups and their specifications are explained in more detail in chapter *2.2.1 Pharmacologic and Surgical Interventions*.

The pathogenesis of COPD includes various extrinsic and intrinsic factors which interact as the disease progresses and contribute to a worsening of the condition in the form of a downwards spiral. It is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in the individual patients [44]. The main cause is tobacco smoking which makes COPD a preventable and treatable, but not curable disease. Therefore the key component in the therapy of COPD is smoking cessation. An overview of the various aspects of the pathogenesis of COPD is given in figure 3.

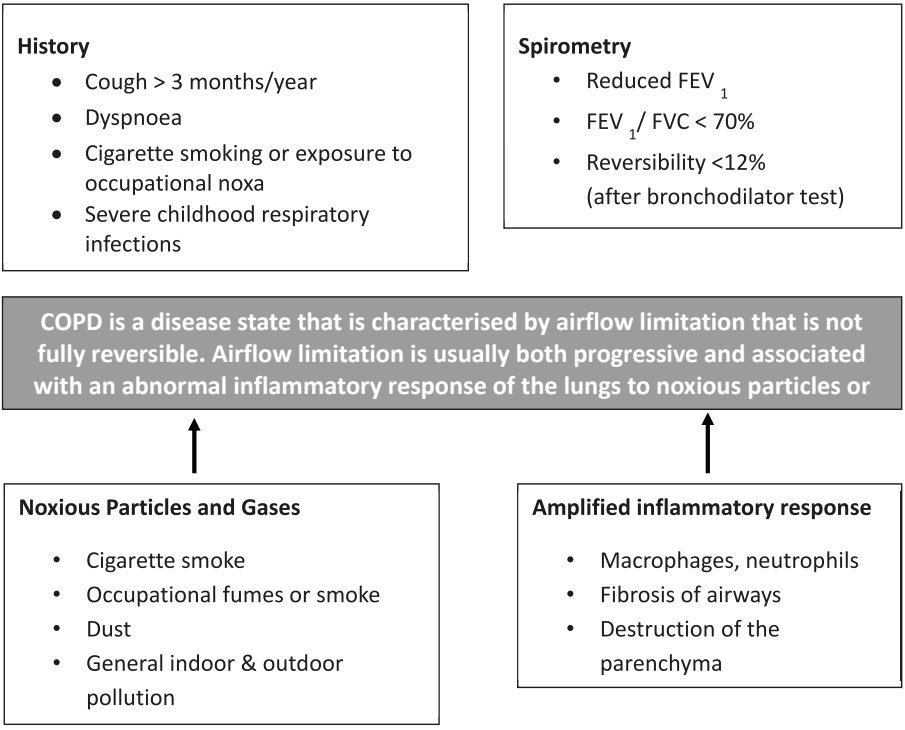

Figure 3: Overview of the pathogenesis, diagnostic and pathophysiological aspects of COPD.

PATHOPHYSIOLOGY AND SYMPTOMS

COPD is by definition, a long-term condition in which the airways and/or the lung tissue is damaged, causing obstruction, narrowing and possibly emphysema. The effects of these pathophysiological changes are reflected in an almost irreversible impaired lung function, which can be measured by spirometric testing using the before said FEV_1. A typical volume-flow-curve of a COPD patient is shown in figure 4.

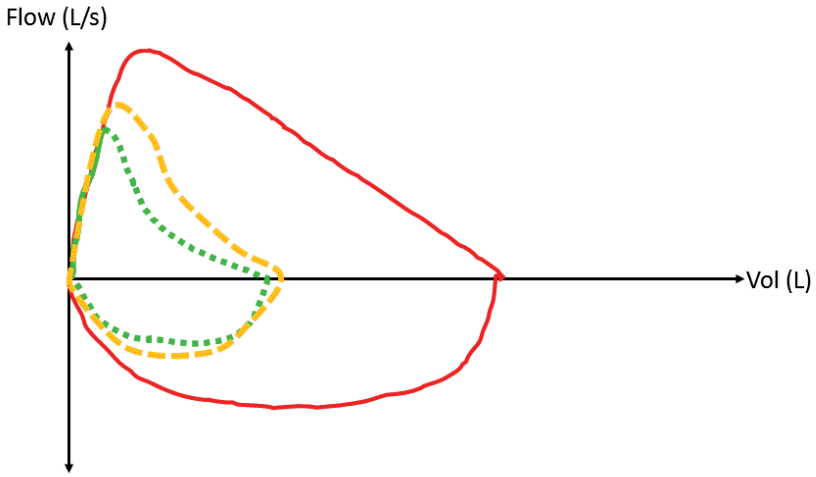

Figure 4: Typical flow-volume curve of a COPD patient. The continuous red line presents a normal flow-curve with the green dotted line showing the impaired respiratory performance of a COPD patient without the use of bronchodilating drugs and the orange dashed line presenting the flow-volume curve of the same patient 20 minutes after applying a bronchodilator. There is a measurable increase of respiratory performance which is normally less than 12% in COPD patients – contrary to asthma where increases of more than 20% are usually found.

The obstruction and destruction of tissue in COPD increases the respiratory resistance. As resistance is increased a greater difference between atmospheric and intra-alveolar pressure must be achieved, through respiratory muscle exertion, to drive air in and out of the lungs. The elastic structures of the smaller bronchioles are damaged, which in return supports the obstruction.

As the disease process continues, the increase in work of breathing will contribute to the overall increase in demand for oxygen within the body. Even whilst resting,

the costs of ventilation may be three to four times that of healthy individuals and, in severe cases, can rise to account for as much as 40% of an individual's total energy expenditure. This situation produces a metabolic response and a reluctance to pursue any physical activity or exercise which in return promotes the catabolic situation of the metabolism and leads to a vicious cycle consisting of dyspnoea, deconditioning and further lung impairment and progression of COPD as demonstrated in figure 5.

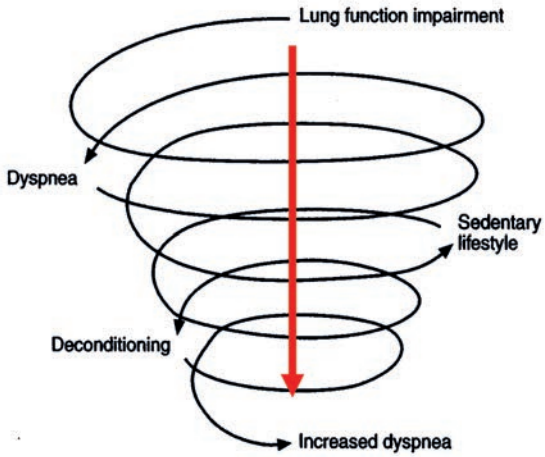

Figure 5: Vicious circle of COPD.

Systemic Features of COPD

It is increasingly recognised that most patients with COPD have comorbidities of a systemic nature that have a major impact on the quality of life and their survival [53]. Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. Inflammatory mediators in the circulation are supposed to contribute to skeletal muscle wasting and cachexia, and could potentially initiate or worsen comorbidities such as ischemic heart disease, chronic heart failure, osteoporosis, diabetes, metabolic syndrome and others [11]. Various aspects of the systemic effects of COPD will be addressed in more detail, as they are paramount to any specific exercise therapy intervention.

As previously mentioned, the lung pathology affects the whole of the system - including fibre type changes in skeletal muscles and general muscle atrophy. Whilst these systemic effects are prominent in individuals with pulmonary disease they are by no means exclusive to these conditions and they may also occur in individuals with chronic heart failure.

When blood oxygen levels are chronically low, a state of chronic hypoxia develops. This could be deemed to have a resulting effect on all organs and subsequently reduces the capacity for the body to work efficiently. One of the most relevant deconditioning effects in COPD can occur in the myocardium. COPD patients tend to have difficulties increasing right ventricular output, and therefore, cardiac output overall is affected. Chronic pulmonary hypertension caused by emphysema and respiratory resistance can have consequential effect on the right ventricle which eventually may lead to right ventricular heart failure.

The chronic inflammation involving $CD8^+$ Tc1 lymphocytes which are cytotoxic (present only in smokers who develop the disease) [54] as well as elevated levels of neutrophils, in return produces high cortisol levels as an anti-inflammatory reaction. This state of permanent inflammation alters the chemical and cellular balance in the cells and subsequently contributes to the dysfunction of the muscular system as a whole. A significant number of male patients show disease specific low blood testosterone levels [55,56,57,58] and in most COPD patients reduced levels of IGF-1 growth hormones can be found [59]. Both testosterone and growth hormones play a key anabolic role in skeletal muscle development. Growth hormone levels will deplete with age in the general population and this can cause age related changes in muscle. The extent of depletion in this population, however, is in excess of general age related reduction and it is considered to be an important factor of muscle dysfunction in COPD patients. Additionally steroid treatment contributes to these effects.

Skeletal muscle dysfunction is therefore a common effect of COPD. Individuals can display a marked decrease in muscular strength and endurance and an increased level of fatigability. This can be explained by the general process of muscle wasting or sarcopenia, but also by a shift in muscle fibre typology with a decrease in the fatigue resistance slow twitch type I fibres [60,61] and a significant increase of type IIX fibres were found in COPD patients [62] which is comparable to the increase of type 2A fibres found in CHF patients [63]. GOSKER et al. (2007) were able to establish in a meta-analysis the correlation between loss in type I fibres and disease severity in COPD, as well as determining reference values for fibre type proportions in healthy subjects in the typical age range for COPD GOLD

stages 3 to 4 (60-70 years) for the vastus lateralis muscle and COPD patients. Individual studies consistently show a reduced proportion of type I fibres that was clearly confirmed in the meta-analysis by revealing a mean difference of 22% in the inter-study analysis and a mean difference of 18% in the intra-study analysis. Likewise, the proportion of fibre type IIX which was 13% higher in patients with COPD in both analyses [64].

Other underlying factors contributing to the muscle wasting in COPD patients are the chronic hypoxia caused by changes in lung pathology, encouraging a fibre type shift along the spectrum towards less aerobic fibres and hypercapnia (high CO_2 levels) occurring as a consequence of the hyperinflation of the lung and impairing the patient's ability to clear the lungs of CO_2. This encourages skeletal muscles to rely on anaerobic capacity, which in turn reduces exercise tolerance. The widespread inflammation which accompanies COPD requires a significant utilisation of energy from the body. In order to produce the proteins involved in the inflammatory process, amino acids are required for synthesis. This in turn depletes the amino acids which are then available for muscle protein synthesis which then leads to muscle atrophy.

This also often results in a low BMI in COPD patients despite an often normal calorie intake. The patients therefore present a low percentage of fat free mass and it is often difficult to increase muscle mass in this group of individuals. A low BMI is considered to be a significant factor in life expectancy in individuals with COPD [65]. However, according to SCHOLS et al. (2005) fat-free mass is supposed to be a better predictor of mortality and thus a marker of systemic disease than BMI in COPD patients [66].

There are a variety of aspects that can contribute to weight loss in this group such as recurrent exacerbations, prolonged periods of immobility and poor calorie intake. Patients with COPD expend more energy when breathing. Inhalation and exhalation are more difficult and require more muscular input which increases energy expenditure. This leads to an increased Basal Metabolic Rate (BMR) and therefore the need to increase the calorific intake to compensate. However, due to the patients' dyspnoea, some individuals may find it difficult to eat as they may also utilise their mouth to breath. Other factors observed in this group of individuals, is a tendency to feel an early satiety which can also be perpetuated by items such as systemic inflammation and hypoxia along with the effects of drugs that increase the metabolic rate such as bronchodilators (β2-mimetics) and all eventually provoke a significant effect on the BMI and any anabolic process including muscle hypertrophy.

2.2 Therapy

The aforesaid systemic effects of CHF and COPD build the foundation for any therapeutic intervention and the understanding of these processes is paramount for developing specific exercise interventions which can produce relevant results for the patients and the health care system. The pharmaceutical and surgical therapy options in both conditions are briefly described in the following chapters and in more depth, discussing the current state of evidence based exercise interventions in the treatment of CHF and COPD.

CHF

The short-term therapy goals for a patient with heart failure are to relieve symptoms and improve the quality of life. The long-term goal of therapy should be to prolong life by slowing, halting, or actually reversing the progressive left or right ventricular dysfunction that is characteristic of the syndrome. The key role in this context, is a potential vicious cycle of heart failure, which is mainly characterised by an increase of symptoms during physical activity (pa), therefore the patient avoids pa and this initiates de-conditioning processes which lead to a further loss of functional capacity on all levels, including skeletal muscle mass, catabolic hormonal changes and an increase of cardiac specific symptoms.

Therefore, the management of heart failure can no longer be confined to the relief of symptoms. The processes that contribute to left ventricular and in some cases to right ventricular dysfunction, may progress independently from the development of symptoms. Treatment to prevent or delay the progression of left ventricular dysfunction may therefore be quite different from the treatment aimed at relieving symptoms and improving the patients' quality of life.

However, the symptoms of CHF are only weakly related to the severity of ventricular dysfunction - although the dysfunction itself is closely linked to mortality. Hence, the sympathetic activation with its vascular, metabolic and renal effects plays an important role in this context and is also reflected in the complex medication scheme of CHF patients. Figure 6 illustrates the interrelationship of these factors that eventually lead to a worsening of CHF.

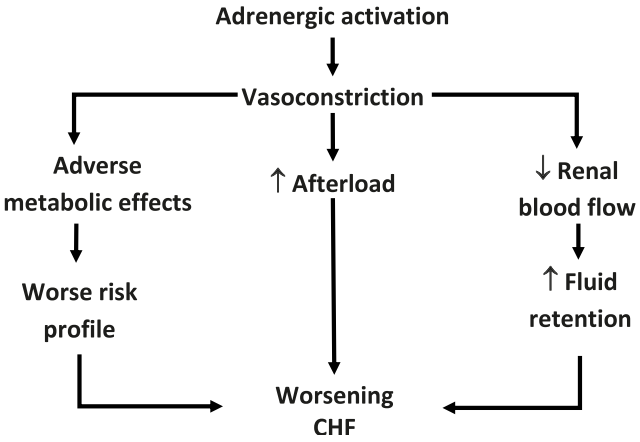

Figure 6: Sympathetic activation and its peripheral, renal and metabolic effects.

The diagram explains why a complete change of the medication scheme in the treatment of CHF was conducted in the 1980s when this interrelationship was discovered and as a consequence introduced beta-blockers as the standard drug for treating CHF.

COPD

The overall targets of therapy in treating COPD is very similar to CHF and includes relief of symptoms, improving health related quality of life (HRQL) and slowing and/or halting the progression of the disease. However, the multi-morbidity of these patients also needs to be addressed in a specific therapy scheme. Some of these morbidities are directly linked to COPD, others to lifestyle (tobacco smoking) or age. Patients with COPD therefore often have complex medical problems including cardiovascular disease such as CHD, heart failure or osteoporosis, diabetes and musculoskeletal problems.

Considering the pathogenesis of COPD, the main intervention in treating this disease is smoking cessation because it is regarded as the foremost cause for COPD. This is also linked to diseases such as CHF as tobacco abuse also causes other health problems such as circulatory problems, cardiac disease and diabetes. Children raised by tobacco abusers have an increased risk of developing asthma which in itself can contribute to developing COPD. There is evidence to illustrate that early cessation can minimise health problems and reduce the decline in lung function [67]. This is illustrated in figure 6 based on a study by FLETCHER and PETO showing the effects of smoking cessation on pulmonary function, disability and mortality.

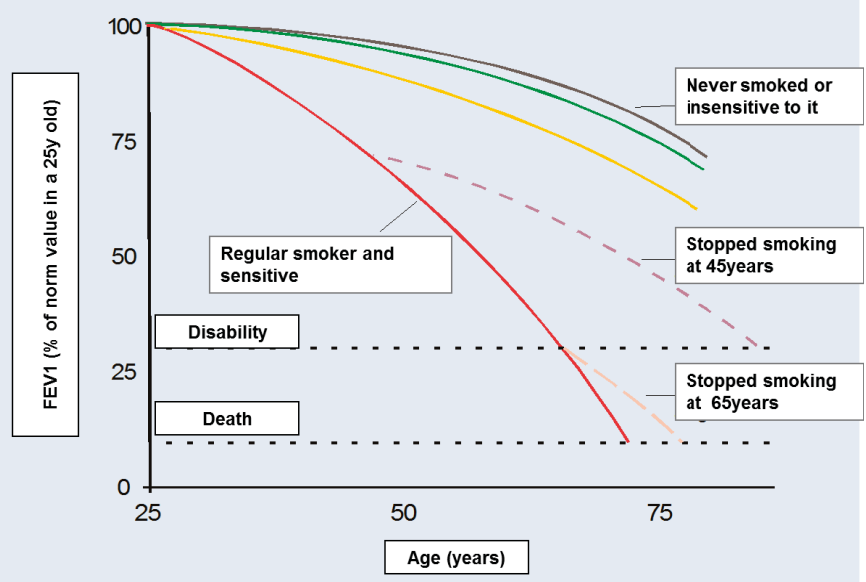

Figure 7: The long-term effects of smoking and tobacco abuse cessation at different ages. (adapted from Fletcher C and Peto R, 1977) [67]

2.2.1 Pharmacological and Surgical Interventions

CHF

The drug treatment in CHF aims at improving symptoms and prolonging life. Thus, the following medication groups are recommended by the ESC for the treatment of CHF: ACE-Inhibitors, ARBs, Aldosterone Antagonists and β-Blockers [43]. Diuretics are also used in most patients as a life prolonging drug. The importance of diuretic therapy can be explained by the cardiac and also renal effects of the adrenergic activation (see figure 6). Hence, diuretics decrease the end diastolic volume, decrease systemic vascular resistance, increase cardiac output/stroke volume, decrease congestive symptoms and thereby can increase exercise capacity in CHF patients.

There are various ways of administering these drugs which include – orally, either as tablets or capsules which are swallowed. This is the most common way of taking cardiac medication; sublingually – when a tablet is placed under the tongue and dissolves; as an aerosol (directly under the tongue); self-adhesive patch (the drug is absorbed over a period of time) or in emergencies or during hospitalisation – intravenously (in a diluted form through an intravenous drip), intramuscularly or subcutaneously.

The following chart presents the guidelines of the European Society of Cardiology for the drug treatment of CHF.

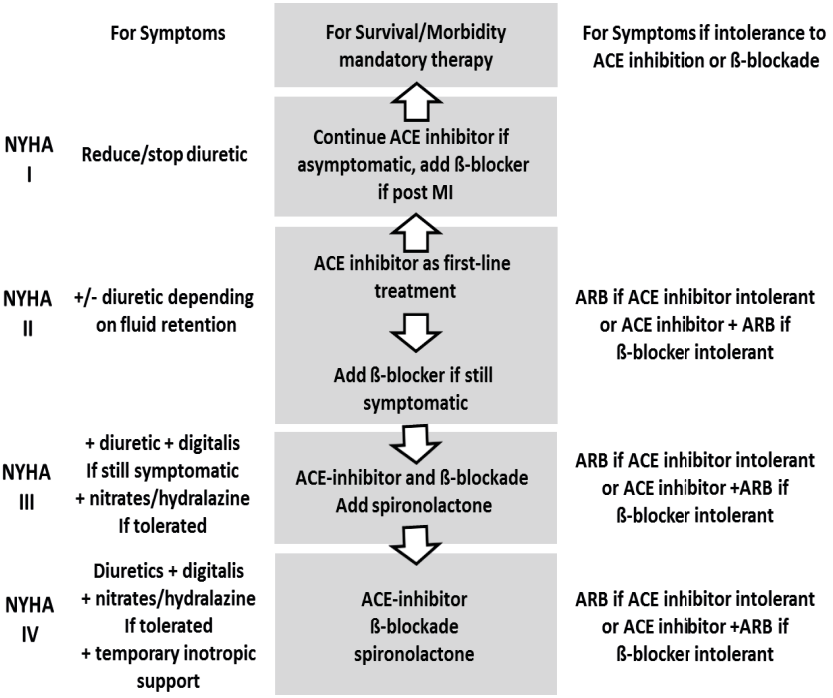

Figure 8: ESC medication guidelines for CHF. [43]

The main medication groups for the treatment of CHF according to the ESC (figure 8) and their effects are described below.

Angiotensin-converting enzyme inhibitors (ACEIs)

The positive effects of ACEIs in the treatment of CHF has an evidence level A which makes it a standard drug in NYHA stage III and IV CHF patients. ACEIs improve ventricular function and patient well-being, reduces hospital admission for worsening CHF, and increases survival. Unless contraindicated or not tolerated, an ACEI should be used in all patients with symptomatic heart failure and a LVEF ≤ 40%.

In hospitalised patients, treatment with an ACEI should be initiated before discharge [43]. Contraindications for the use of ACEIs are: a history of angioedema, bilateral renal artery stenosis, serum potassium concentration >5.0 mmol/L and/or a severe aortic stenosis [43].

β-Blockers

The use of β-blockers in the treatment of CHF has an evidence level A and is therefore strongly recommended. Unless contraindicated or not tolerated, a β-blocker should be used in all patients with symptomatic heart failure and an LVEF ≤40%. Although the use of beta-blockers is generally recommended in all stage II to IV CHF patients according to the ESC guidelines which therefore also include patients with an LVEF greater than 40%. β-blockade improves ventricular function and patient well-being, reduces hospital admission for worsening CHF, and increases survival. Where possible, in hospitalised patients, treatment with a β-blocker should be initiated cautiously before discharge [43].

Contraindications for the use of β-blockers are: asthma - although COPD is not a contraindication, second- or third-degree heart block, sick sinus syndrome (in the absence of a permanent pacemaker), sinus bradycardia (<50 bpm) [43].

Aldosterone antagonists

Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF ≤ 35% and severe symptomatic HF, i.e. currently NYHA functional class III or IV, in the absence of hyperkalaemia and significant renal dysfunction. Aldosterone antagonists reduce hospital admission for worsening HF and increase survival when added to existing therapy, including an ACEI. According to the ESC in hospitalised patients satisfying these criteria, treatment with an aldosterone antagonist should be initiated before discharge [43]. The level of evidence for the use of aldosterone antagonists in improving the cardiac situation of CHF patients is B.

Contraindications for this drug as part of a CHF medication scheme are: serum potassium concentration >5.0 mmol/L, serum creatinine >220 mmol/L (~2.5 mg/dL), concomitant potassium sparing diuretic or potassium supplements, combination of an ACEI and ARB [43].

Angiotensin receptor blockers (ARBs)

Unless contraindicated or not tolerated, an ARB is recommended in patients with HF and an LVEF >40% who remain symptomatic despite optimal treatment with an ACEI and β-blocker, unless also taking an aldosterone antagonist. Treatment with an ARB improves ventricular function and patient well-being, and reduces hospital admission for worsening HF.

There is a level A evidence for ARBs reducing the risk of death from cardiovascular causes in CHF patients and level B evidence for ARBs as an alternative in patients intolerant of an ACEI. In these patients, an ARB reduces the risk of death from a

cardiovascular cause or hospital admission for worsening heart failure. In hospitalised patients, treatment with an ARB should be initiated before discharge [43].

Contraindications are as with ACEIs, with the exception of angioedema. Also patients treated with an ACEI and an aldosterone antagonist. An ARB should only be used in patients with adequate renal function and a normal serum potassium concentration.

Further Pharmacological Options

Further pharmacological options are *nitrates* which are used to relieve acute symptoms by causing venodilatation, thereby reducing the amount of blood returning to the heart and consequently the myocardium's workload. Fast-acting nitrates can be administered sublingual to relieve acute angina or as an aerosol; *Digoxin* may also be used in patients with symptomatic HF to slow a rapid ventricular rate; *Diuretics* are recommended in CHF patients with clinical signs or symptoms of congestion – diuretics have level B evidence in this context; *Antiplatelet agents* which are not as effective as warfarin (anticoagulant) are also used to reduce blood viscosity; HMG CoA reductase inhibitors or so called *statins* are predominantly prescribed to elderly patients with symptomatic chronic HF and systolic dysfunction caused by CAD in order to reduce cardiovascular hospitalisation.

Surgery

The rationale for a coronary angiography and/or left ventriculography is to identify high risk patients in whom coronary angioplasty and subsequent revascularisation might improve survival. Such a strategy can be effective only if the patient's prognosis on medical therapy is sufficiently poor that it can be improved.

Therefore, if clinical symptoms of CHF are present, surgical correctable conditions should be identified and corrected if indicated. As CAD is the most common cause of CHF and is present in 60–70% of patients with HF and impaired LVEF [43] revascularisation in patients with heart failure is a common procedure. Both a coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) should be considered in selected CHF patients with CAD. The decision for the choice of the method of revascularisation needs to be based on a careful evaluation of co-morbidities, procedural risk, coronary anatomy, LV function, and the presence of haemodynamically significant valvular disease [43]. There is evidence that in heart failure of ischaemic origin, revascularisation may lead to symptomatic improvement and potentially improve cardiac function [69].

CABG

In this procedure the narrowed sections of coronary arteries are bypassed by grafting a blood vessel between the aorta and a point in the coronary artery beyond the narrowed or blocked area. A section of vein removed from the leg is used for the bypass channel or graft, but increasingly the two arteries that run down the inside of the chest wall are also used. Coronary bypass surgery is considered a standard procedure nowadays.

Pacemakers

The conventional indications for patients with normal LV function also apply to patients with CHF. In patients with heart failure and sinus rhythm, maintenance of a normal chronotropic response and coordination of atrial and ventricular contraction with a DDD pacemaker is especially important [43]. In CHF patients with concomitant indication for permanent pacing and NYHA class II–IV symptoms a cardiac resynchronisation therapy (CRT) with pacemaker function (CRT-P) should be considered. CRT-P is recommended to reduce morbidity and mortality in patients who are symptomatic despite optimal medical therapy, and who have a reduced EF (LVEF <35%) and QRS prolongation [43].

Implantable cardioverter defibrillator

Implantable cardioverter defibrillator (ICD) therapy for secondary prevention is recommended for survivors of ventricullar fibrillation. An implantable cardioverter defibrillator or ICD is a small device which can be surgically implanted. Like a normal defibrillator it can deliver a shock to a heart which is beating too slow or too fast, in order to restore a normal rhythm. It monitors the electrical signals in the heart. Therefore it can track the heart rhythm and when a shock is required, deliver it automatically.

Heart transplantation

The first heart transplant was carried out in South Africa in 1967. In Europe transplants are now carried out on a regular basis especially in NYHA IV heart failure patients. The number of heart transplants is limited by the number of donor organs available. The risk of a heart transplant is significantly less than a lung transplant. Heart transplantation is therefore an accepted treatment for end-stage CHF. Although controlled trials have never been conducted, there is consensus that transplantation, provided proper selection criteria are applied, significantly increases survival, exercise capacity, return to work, and quality of life compared with conventional treatment [43].

COPD

Medication is an important part of the management of COPD, but less affective without smoking cessation which is the foremost important intervention. The aims of pharmacologic therapy in COPD are to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. This is achieved by reducing inflammation, swelling and sputum in the airways and thereby reducing unpleasant symptoms such as dyspnoea or the exacerbation rate. However, as most drugs are inhaled, it is important that the COPD patients are competent in the correct use of inhalers and are also taught to use breathing control as part of the inhaling process as well as positions of ease to cope with episodes of breathlessness in conjunction with their inhalers.

The incorrect use of inhalers is a common problem amongst COPD and asthma patients and reduces the effectiveness of any medication scheme in this population significantly. An educational module on how to use aerosols and inhalers correctly is therefore an integral part of any COPD disease management.

A variety of medications used in the treatment of COPD are used at different stages of the disease. Some medications are required to be taken consistently where as others are relievers which can be taken when an exacerbation of symptoms occurs i.e. Salbutamol inhalers for Asthma. There are different modes of delivery: some drugs are oral, but most are inhaled. Inhaled drugs have the advantage of being deposited directly into the lungs. With only small amounts of the drug being absorbed into the blood stream, there are less systemic side effects.

COPD patients are not only categorised by their symptom severity and FEV_1 limitations, but also for therapy purposes by their risk. GOLD therefore developed a model for symptom/risk evaluation of COPD patients in order to identify and reduce exposure to risk factors – especially for unwanted side effects of medication [46]. These groups are divided into four groups A, B, C and D. These again relate to the GOLD classification of COPD – similar to the AHA system in CHF which relates to the NYHA classification.

Group A patients have few symptoms and a low risk of exacerbations. Specific evidence for the effectiveness of pharmacologic treatments is not available for patients with $FEV_1 > 80\%$ predicted (GOLD 1) [46].

Group B patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are superior to short-acting bronchodilators and are therefore recommended [46].

Group C patients have few symptoms but a high risk of exacerbations. Thus a fixed combination of inhaled corticosteroid/long-acting beta$_2$-agonist or a long-acting anticholonergic is recommended [46].

Group D patients have many symptoms and high risk of exacerbations. The first choice of therapy is inhaled corticosteroid plus long-acting beta2-agonist or long-acting anticholonergic. As an alternative choice a combination of all three class drugs is recommended [13].

Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function which is the hallmark of this disease. Nevertheless, pharmacological interventions form an essential and effective treatment of COPD. A proposed model for initial pharmacological management of COPD according to the individualised assessment of symptoms and exacerbation risk is shown in table 8.

Table 8: Proposed pharmacological therapy scheme for COPD by GOLD 2010. [46].

Initial Pharmacologic Management of COPD			
Patient Group	**Recommended First Choice**	**Alternative Choice**	**Other Possible Treatments**
A	Short-acting anticholinergic pm *or* Short-acting beta$_2$-agonist pm	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist *or* Short-acting beta$_2$-agonist and Short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist	Long-acting anticholinergic and long-acting beta$_2$-agonist	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long -acting beta$_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta2-agonist and phosphodiesterase-4 inhibitor	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline

D	Inhaled corticosteroid + long -acting beta$_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long -acting beta$_2$-agonist and Long-acting anticholinergic *or* Inhaled corticosteroid + long -acting beta$_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline

Following, the most commonly used drugs in the pharmaceutical treatment of COPD are presented in more detail.

Bronchodilators

Bronchodilators reduce the constriction of the airways and maintain the airways open and thus improve ventilation. There are wide ranges of bronchodilators, which can be prescribed, and they have different modes of action, but are usually inhaled as an aerosol or powder. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators (Evidence A) [46].

Short Acting β_2 Agonists, e.g. Salbutamol cause bronchodilation. These only take a few minutes to exert their effects and last a few hours. These are also prescribed for COPD, chronic bronchitis and asthma [52]. Bronchodilators are prescribed as a reliever to reduce symptoms within minutes.

Long Acting β_2 Agonists medications, exert similar effects to Short Acting β_2 Agonists, with their duration being much longer. It takes 20 minutes before a relief of symptoms is displayed and can last up to 12 hours. Again they are prescribed to induce bronchodilation in patients with COPD, chronic bronchitis and asthma.

Short Acting Anticholinergics, assist to maintain the airway as dilated as possible, but rather than cause dilation, they inhibit constriction. Inhibiting cholinergic effects, which lead to constriction, instigates this [52]. They are rapid acting and can last up to 6 hours. Long Acting Anticholinergics drugs, work in the same way as Short Acting Anticholinergics however, their duration is much longer i.e. up to 24 hours. Spiriva is a medication commonly prescribed. It is taken as one dry powder capsule per day [52].

For both beta$_2$-agonists and anticholonergic, long-acting formulations are preferred over short-acting formulations (Evidence A). The combined use of short- or long-acting beta2-agonists and anticholonergic may be considered if symptoms are not improved with single agents (Evidence B) [46].

Theopyhlline is also a bronchodilator which comes in tablet form rather than being inhaled. This substance is the oldest bronchodilator known to mankind as it is contained in its natural form in tea and was even prescribed in ancient Greece.

Based on evidence of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (Evidence B) [42].

Corticosteroids

Corticosteroids are inhaled anti-inflammatory medications, which can be used during exacerbations, however they are not recommended for maintenance with the exception of severe and very severe COPD patients. Currently long-term treatment with inhaled corticosteroids is therefore only recommended for GOLD III and IV patients and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (Evidence A) [46]. However, there is a small group of COPD patients who are classed as non-responders, but there is no evidence to recommend a short-term therapeutic trial with oral corticosteroids in patients with COPD to identify those who will respond to inhaled corticosteroids or other medications.

Long-term mono-therapy with inhaled corticosteroids is not recommended in COPD because it is less effective than the combination of inhaled corticosteroids with long-acting beta$_2$-agonists (Evidence A) [46]. Also common side effects need to be taken into consideration when prescribing a long-term medication scheme with corticosteroids. Side effects include adrenal suppression, osteoporosis, skin thinning, muscle wasting, mood changes and acne. Furthermore, a chronic use of corticosteroids eventually reduces sensitivity to the medication and higher doses are necessary. Furthermore, long-term treatment containing inhaled corticosteroids should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure [13].

Considerations for COPD Patients with CHF

It is important to be aware of medications that patients may be taking for co-morbidities. For example COPD patients with an element of heart failure may be given diuretics to reduce fluid retention. This might cause dyspnoea as there is a

high correlation between dehydration and breathlessness. Hence breathing problems may be exacerbated in these patients.

Oxygen Therapy

COPD-patients who show low oxygen levels ($SaO_2 \leq 88\%$) at rest benefit from long term oxygen therapy (LTOT) for 15 hours per day [52]. Some patients drop their oxygen levels when exercising. This is measured by recording pulse oximetry (saturations) during walking tests. The normal saturation or SaO_2 (percentage of available haemoglobin that is saturated with oxygen) level is between 92-98%. Individuals who present with a $SaO_2 \leq 88\%$ whilst breathing room air or PaO_2 (partial pressure of oxygen in arterial blood) is ≤ 55mmHg should be considered for LTOT [46]. Oxygen will be supplied via a small portable or lightweight cylinder.

Surgery

Postoperative pulmonary complications are as important and common as postoperative cardiac complications and therefore are a key component of the increased risk posed by surgery in COPD patients. The main factors contributing to the risk include smoking, poor general health status, age, obesity and COPD severity [46].

In extreme cases, sufferers of Emphysema may be advised to undergo lung volume resection surgery to prolong life expectancy. Resection surgery is an inclusion criteria for patients suitable for rehabilitation. Lung transplantation might also be a necessary intervention. However, the mortality rate of lung transplantation is still very high. Thus this is a last resource when the patient's life is at risk. This is usually the case when the FEV_1 permanently falls below 20%.

For lung resection, the individual patient´s risk factor should be identified by careful history, physical examination, chest radiography, and pulmonary function test. There is a consensus that all COPD candidates for lung resection should undergo a complete battery of tests, although the value of pulmonary function tests in this context remains contentious [46].

2.2.2 Exercise Therapy

For many CHF and COPD patients, the medical history usually consists of a progression of symptoms that follows on to disability and death from heart failure and/or respiratory failure. This respectively happens at a relatively early age [70,71]. Although the underlying pathology is initially confined to myocardium and/or the lungs, the associated physical deconditioning and the emotional responses to chronic cardiac and respiratory disease contribute greatly to the resulting

morbidity. Hence, exercise therapy is an integral part of rehabilitating both conditions and reversing the deconditioning process and improving symptoms and general morbidity – possibly even reducing mortality.

Exercise therapy is therefore defined as – "… medically indicated and prescribed exercise with behaviour orientated components, planned and dosed by therapists, controlled together with the doctor and carried out with the patient either alone or in a group. It aims to rehabilitate physical, mental and psycho-social impairments (affecting daily life, leisure time and work) or guard against damage and risk factors with suitable activities from sport, exercise and behavioural orientation" [72] (DVGS, 2013).

Rehabilitation is defined as a treatment or treatments designed to facilitate the process of recovery from injury, illness, or disease to as normal a condition as possible. The purpose of rehabilitation is to restore some or all of the patient's physical, sensory, and mental capabilities that were lost due to injury, illness, or disease [73].

Although official organisations in North America and Europe have endorsed cardiac and pulmonary rehabilitation as integral to the long term management of conditions such as CHF and COPD [74,53], reports describing the benefits of rehabilitation have, until recently, been from trials that were uncontrolled and programmes that were unsupervised. When controlled trials have been reported, they have been limited by the lack of standardised measurements of exercise tolerance and especially quality of life [75,76]. Given the commitment asked of the patients, their families and the health care professionals involved in their care, the multiple interventions made, should be justifiable by demonstrating an improvement in quality of life and exercise tolerance attributable to the rehabilitation programme.

One of the main practical problems in rehabilitation is the lack of sports medicine knowledge and exercise experience of physicians complicating the scenario as they typically prescribe aerobic exercise - and particularly walking - for the purpose of avoiding further heart or respiratory complications which is not addressing the complex physiological symptoms of CHF and COPD specifically enough, but are usually practiced at an intensity that is ineffective for provoking any anabolic responses. Therefore these recommendations are inadequate for these patients in order to be able to return to activities of daily living (ADL), such as mowing the lawn, lifting grandchildren or vacuum cleaning. The following statement of Adams et al. (2006) [77] summarises this problem:

"…. While physicians now acknowledge the value of exercise in cardiac rehabilitation, they have been hesitant to allow resistance training. Part of the problem is the existing guidelines. In our opinion, these guidelines not only delay resistance training unnecessarily but also prescribe weight amounts that are below what patients need for even the most basic activities of daily living. We argue that resistance training should be promoted following the principle of specificity—that is, based on the fact that most patients set goals not to run a 10-kilometer race or to go mountain biking but rather to rise from the bathtub or mow the lawn. The constraints faced in cardiac rehabilitation, from physician prescriptions and from the guidelines, are particularly worrisome, since in society today we seem to place more importance on specifically training athletes (cyclists, marathon runners, football players) than we do on appropriately preparing patients to safely perform everyday activities. This limitation has become particularly obvious as cardiac rehabilitation patients have become younger. Some of these patients need to return to firefighting, police work, or other physically stressful jobs."

In the following, firstly, the role of exercise and general aspects of each condition will be addressed; secondly, guidelines of different national and international bodies for the rehabilitation of CHF and COPD will be presented and thirdly, evidence for exercise training and/or rehabilitation of heart failure and COPD will be analysed in the form of meta-analysis as well as specific exercise interventions which are structured into endurance exercises, strength exercises, mixed exercise interventions and others.

CHF

Physical inactivity is common in patients with CHF and contributes to its progression. A key role in this context plays the so called vicious cycle of heart failure, which is mainly characterised by an increase of symptoms during physical activity, therefore the patient avoids physical activity and this initiates deconditioning processes which lead to a further loss of functional capacity on all levels, including skeletal muscle mass, catabolic hormonal changes and an increase of cardiac specific symptoms [78,79,80,81].

The World Health Organization has defined cardiac rehabilitation as "the sum of activities required influencing favourably the underlying cause of the disease, as well as the best possible, physical, mental and social conditions, so that they (people) may, by their own efforts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an

isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facet" [82].

Regular, initially supervised, resistance or endurance training improves autonomic control by enhancing vagal tone and reducing sympathetic activation, improves muscle strength, vasodilator capacity, and endothelial dysfunction, and decreases oxidative stress [43]. Several systematic reviews and meta-analyses of small studies have shown that physical conditioning by exercise training reduces mortality and hospitalisation when compared with usual care alone, and improves exercise tolerance and health-related quality of life [83,84,85,86].

Thus, cardiac rehabilitation programmes following a cardiovascular event or episode of decompensation represent an effective treatment option for patients with CHF. Professional associations such as the ESC, AHA and ACC therefore recommend exercise training to all stable chronic heart failure patients. There is no evidence that exercise training should be limited to any particular CHF patient subgroups such as NYHA class, LVEF or specific medication groups. Exercise training programmes appear to have similar effects whether provided in a hospital or at home [10]. It still remains unclear whether certain exercise interventions have specific benefits for some of these subgroups, i.e. severity specific according to NYHA classes.

The position paper of the European Society of Cardiology from 2003 underlines the important role of systematic exercise by providing a summary of the relationships between physical activity and cardiovascular health in primary and secondary prevention. However, the recommendations simply reinforce the existence of a "treatment gap", i.e. the difference between the current evidence for effective interventions and the actual service and care that patients receive regarding structured exercise in an out-patient setting led by qualified specialists as part of a continuing rehabilitation and/or secondary prevention process.

A prime example for the poor state of cardiac rehabilitation in general was reflected by findings of BRODIE et al. [87] who analysed the rehab situation in England in 2006. The study gave a detailed analysis of cardiac rehabilitation programmes in England to compare actual provision with the recommendations of the National Service Framework guidelines. The results noted major discrepancies between programmes and the national recommendations. Perceptions of the service were often varied within key trust staff. Staffing levels, lack of facilities and space were identified as a weakness in many of the programmes. Inadequate exercise sessions, poor record keeping and a failure to

tailor the sessions to the patients' needs were common. Mean funding was £288 per patient rehabilitated. The conclusion was that for those 30% of eligible patients who enter cardiac rehabilitation in England, the service suffers from inadequate staffing, facilities and space, associated with gross under funding. If the recommended 85% of eligible patients were included, the situation would be much worse. The Department of Health recommendations for cardiac rehabilitation have not been translated into action, with most hospitals giving it low priority compared with other cardiology services.

The situation in Germany regarding accessibility and number of cardiac rehabilitation programmes is with over 6000 comparably better than in England. This however, does not refer to the quality of the programmes as there is no nationwide quality management procedure in place and to date no comparable study to the above has been published analysing the current situation and quality of cardiac rehabilitation programmes in Germany. It must be therefore assumed that the situation is similar to England.

This problem is partially due to the circumstance when patients traditionally were recommended to avoid physical exercise. This was because it was believed that the strain might aggravate the cardiac condition and therefore is harmful – especially for the high risk population of CHF patients. This view was adopted by the general public and also the political decision makers and most managers in the health care systems and even doctors. This belief however has been challenged in the last two decades and several studies proved the positive effects of exercise training in CHF patients [88,89,90,91,92,93]. Most studies used an endurance training intervention; few investigated the effects of strength training exercises [94,95,96]. The other explanation for the above problem is the lack of qualified exercise specialists, especially in the field of CHF.

However, the results of other long term intervention studies prove the safe feasibility of different outpatient training interventions and suggest specific positive adaptations in patients with chronic heart failure [97,98,99].

Guidelines

German guidelines for the rehabilitation of patients with cardiovascular diseases (CHF extract) [100]:

"… a further task (of rehabilitation in CHF) is initiating a physical training. A prerequisite is an optimised medication scheme as well as the stabile situation of the patient for at least 3 weeks. The basis of an exercise therapy is aerobic

endurance training. The standard is the continuous method; in patients with reduced exercise tolerance interval training may be added. Low intensity dynamic strength training (30-60% 1RM) with a minimal isometric component may be incorporated in addition, but cannot replace endurance training. If necessary respiratory exercises are recommended as well."

German Heart Foundation [101]:

"… For severe chronic heart failure: regular moderate dynamic activity (e.g. walking, cycling) should be carried out five times a week for 20 min or three times a week 30-45 min, i.e. cycling with a load of 40-70% of the maximal heart rate and/or oxygen consumption. Physical efforts that provoke dyspnoea and particularly isometric work, which leads to an increase in peripheral resistance, should be avoided generally. Strict physical indulgence and bed rest are only indicated during an acute and/or de-compensating chronic heart failure."

These recommendations are very general, particularly concerning the indication for training intensities. Also the choice of training modalities remains too general and in the case of resistance/strength training does not relate to the current scientific evidence. Clarification and specification is needed regarding training types and methods as well as concrete intensities referring to the severity stage of CHF.

The *American Association of Cardiovascular and Pulmonary Rehabilitation* (AACVPR) has a more concrete approach by recommending [34] an exercise protocol for CHF patients including a longer warm-up and cool-down, the use of interval exercises (1-6 min) and careful progression as well as encouraging weight bearing for ADL. The exercise training programmes should consist of a variety of modes of exercises for 20 to 60 minutes, 3 to 7 days a week at 40 to 90% of peak HR or oxygen consumption for endurance exercises and strength exercises administered to major muscle groups with an intensity of 60 to 80% of maximum voluntary contraction or of the 10-repetition method (10RM). Circuit training combined with aerobic exercises appears to be safe while providing improvements in peripheral muscle strength and endurance, exercise tolerance, cardiorespiratory function and symptoms.

The *American Heart Association* also recommends strength training using approx. 8-10 different exercises, 1-3 sets with 15 - 20 repetitions and breaks of 30 - 45 seconds, with an intensity of 30 - 50 % of the 1RM (1-Repetitions maximum). The AHA guidelines (2007) go on to state that a comprehensive resistance training programme of 8 to 10 exercises can be accomplished in 15 to 20 minutes and

should be performed after the aerobic component, which will ensure an adequate warm-up.

Even more specific recommendations for the exercise therapy with CHF patients are given by the *Association of Chartered Physiotherapists Interested in Cardiac Rehab* (ACPICR) which is a British professional body. ACPICR guidelines (2009) [102] recommend initially adopting an interval versus a steady state approach, with focus on increasing the peripheral stimulus whilst minimising the CV stress. The guidelines also recommend the combination of cardiovascular and muscular strength and endurance training with low to moderate intensity and dynamic large muscle group work such as walking, stationary cycling (initial intensity may be 40% or less of heart rate reserve, monitored against RPE). Resistance training exercises should target specific muscle groups to assist ADL and function and an interval approach initially employed with work phases of one to six minutes and rest phases of one to two minutes. A work to rest ratio of 1:2 or 1:1 is recommended with an endurance to strength exercise ratio of 1:1 and/or 2:1. In the context of strength training an alternating seated to standing work ratio of 1:1 up to 1:3 is recommended. The guidelines also suggest breathing exercises, breathlessness management and recovery strategies that include some emphases on posture training and core trunk strength.

Meta-Analysis

Advantages of outpatient exercise training are reduced waiting lists, better compliance, reduced time investment by the patient with reduced travel expenses, and less dependence on other people to participate. Meta-analyses of randomised trials have demonstrated gains roughly equivalent to those from beta-blockers, with a 20-25% reduction in total mortality and a 20% reduction in cardiovascular mortality [103].

A systematic review with a meta-analysis by VAN DER MEER et al. (2012) studied the effects of outpatient exercise training programmes compared with usual care on exercise capacity, exercise performance, quality of life, and safety in patients with chronic heart failure [104]. Only randomised controlled trials concerning patients with CHF, with a left ventricular ejection fraction ≤40%, were included. 22 studies were included. The findings showed a significant increase of VO_{2max} in the intervention group of 1.85 ml/kg/min – although it is debatable if VO_{2max} or rather $VO_{2\ peak}$ was measured in these studies; also a significant improvement in the 6-min walking test by 47.9 m was shown, and the health related quality of

life showed significant differences by 6.9 points. In none of the studies was a significant relationship found between exercise training and adverse events. Outpatient exercise programmes therefore must be considered a safe intervention for this population.

Another systematic meta-analysis conducted by DAVIES et al. (2010) focused on health-related quality of life (HRQL), mortality and hospital admissions in patients with systolic heart failure [105]. Randomised controlled trials of exercise-based interventions with six months follow up or longer, compared to usual medical care or placebo were considered. 19 trials with 3647 participants met the inclusion criteria. One large trial recruited 2331 of the participants. There was no significant difference in pooled mortality between groups in the 13 trials with < 1 year follow up. There was evidence of a non-significant trend toward a reduction in pooled mortality with exercise in the four trials with > 1 year follow up. A reduction in the hospitalisation rate was demonstrated with exercise training programmes. Hospitalisations due to heart failure were reduced with exercise and there was a significant improvement in HRQL. One of the most interesting results of this review was the effect of cardiac exercise training on total mortality and HRQL. These were independent of the degree of left ventricular dysfunction, type of cardiac rehabilitation, dose of exercise intervention, length of follow up, trial quality, and trial publication date [105]. Previous reviews showed that exercise training improved exercise capacity in the short term for patients with mild to moderate heart failure when compared to usual care.

An earlier meta-analysis by VAN TOL et al. (2006) looked at CHF patients with an LVEF less than 40% [106]. Studies were included that compared exercise training with standard medical treatment without additional exercise training. Exercise training had to include at least one of the following: walking, cycling or strength training of peripheral muscles. Studies in which only respiratory muscles or one isolated muscle group were trained were excluded. The interventions included were aerobic activities, sometimes combined with callisthenics or ball games, resistance training and interval training. The average training period duration was 13.0 (+/- 7.8) weeks, with a mean session duration of 50.0 (+/- 22.0) minutes and an average frequency of 3.7 (+/- 1.7) times per week. 35 trials (n=1,486) were included - 31 parallel RCTs and 4 crossover trials.

The diastolic BP at rest showed a statistically significant improvement (7 trials, n=209; SES -0.33, 95% confidence interval, CI: -0.61, -0.05, p=0.021) as did end-diastolic volume (9 studies, n=527; SES -0.21, 95% CI: -0.39, -0.04, p=0.017). Cardiac performance during maximum exercise also showed significant changes in

favour of exercise training after a period of maximum exercise for heart rate (18 trials, n=683; SES 0.20, 95% CI: 0.05, 0.35, p=0.011), systolic BP (10 trials, n=382; SES 0.22, 95% CI: 0.02, 0.43, p=0.030) and cardiac output (3 trials, n=104; SES 0.58, 95% CI: 0.19, 0.97, p=0.004), but there was no change in diastolic blood pressure and the authors reported insufficient data to obtain the results of LVEF during exercise. There was also significant improvement in the results for VO_2 (31 trials, n=1,240; SES 0.60, 95% CI: 0.42, 0.79, p=0.000), maximal power output (19 trials, n=715; SES 0.57, 95% CI: 0.42, 0.73, p=0.000), ventilatory or lactic-derived anaerobic threshold (13 trials, n=511; SES 0.84, 95% CI: 0.48, 1.20, p=0.000) and 6-Minute Walking Distance (6-MWD) (15 trials, n=599; SES 0.52, 95% CI: 0.36, 0.69, p=0.000). HRQL was assessed using the Minnesota Living with Heart Failure Questionnaire in which the score decreased significantly from baseline (9 trials, n=463; SES -0.41, 95% CI: -0.60, -0.22, p=0.000) - this favoured training. In conclusion exercise training in stable patients with mild to moderate CHF resulted in statistically significant improvements in maximum heart rate, maximum cardiac output, VO_2, anaerobic threshold, 6-MWD and HRQL. The authors also noted that there was a limitation of the study, as patients with CHF are often older than those included in the meta-analysis and may have additional co-morbidities which limit exercise; this may restrict the generalizability of the review results [106].

Endurance Exercise Interventions

A number of trials suggest that moderate intensity exercise training is safe and progression of exercise should be followed in the order of duration, then frequency, then intensity [107]. WILLENHEIMER (2001) also recommended that exercise training should be continued to result in sustained benefit in this patient group [108]. Overall recommendations are that stable CHF patients should be enrolled into moderate intensity supervised exercise training programmes, in order to give improved exercise tolerance and quality of life.

That said, certain physical activities are contraindicated or cautioned against. A study by MEYER and BÜCKLING (2004) [109] found that immersion in water to the neck created abnormal cardiac responses including left ventricular overload and an inability for stroke volume to increase appropriately. This increases the risk of further ventricular dilation. The study also stated decompensating CHF was an absolute contraindication for immersion in water and swimming.

Endurance training can be performed in different ways using a variety of methods. The most common forms that are also used in cardiac rehabilitation are the continuous principle – again with a range of methods such as fartlek (variable

continuous method). However, there are some physiological and practical reasons why other exercise modalities might be more effective concerning symptoms such as muscle wasting in certain CHF patients. The interval principle, for instance, comprises of the intensive and extensive method which generally use higher intensities than the continuous methods. There is also the repetition principle and/or method which is not commonly used in endurance exercises in a rehabilitation setting due to its very high intensities. Some of these different methods also have been subject to scientific studies with CHF patients and are presented in the following, structured by continuous exercise training and interval training.

CONTINUOUS EXERCISE

Aerobic training using the continuous method was in the past the longest applied exercise modality in cardiac rehabilitation and therefore the most researched one as well. Hence, the evidence in CHF regarding continuous exercises is also very strong. The selection criteria for the presented studies in this context are publication date, type of endurance exercise as well as relevant parameters investigated. However, these studies can only be representative for a wider range of scientific publications which are included in the meta-analysis previously referred to.

BELARDINELLI et al. (1999) investigated the long-term effects of moderate endurance training on CHF [110]. They randomised 94 patients with stable CHF into a control and an intervention group. The intervention group (n=48) underwent a supervised moderate exercise protocol on a cycle ergometer at 60% of peak VO_2, initially three times a week for eight weeks, then twice a week for 1 year. At baseline and at months 2 and 14, all patients underwent a cardiopulmonary exercise test. Significant changes were only observed in patients in the intervention group. Both peak VO_2 and the overall activity score improved at 2 months (18% and 24%, respectively; P<0. 001 for both) and did not change any further after 1 year. Quality of life also improved and paralleled peak VO_2. Exercise training was associated with both, lower mortality (n=9 versus n=20 for those with training versus those without; relative risk (RR) =0.37; 95% CI, 0.17 to 0.84; P=0.01) and hospital readmission for heart failure (5 versus 14; RR=0.29; 95% CI, 0.11 to 0.88; P=0.02). The authors therefore concluded that long-term moderate endurance training determines a sustained improvement in functional capacity and quality of life in patients with CHF.

KILLAVOURI et al. (2000) focused in their investigations on the effects of endurance training on percentage distribution of muscle fibres, on activities of the rate-limiting enzymes of the metabolic pathways and on electrophysiology in skeletal muscles [111]. 27 patients with stable CHF (NYHA class II-III) were randomised in to a training group (n=12) and a control group (n=15). The training group exercised on a bicycle ergometer for 30 min three times a week for 3 months using a load corresponding to 50-60% of their peak VO_2 consumption. This was followed by a 3-month training period at home according to personal instructions (walking, cycling, rowing, and swimming). The muscle histology was studied and the activities of the rate-limiting enzymes were measured of anaerobic glycolysis (phosphofructokinase, PFK), glycogenolysis (phosphorylase), citric acid cycle (alpha-ketoglurate dehydrogenase) and fatty acid oxidation (carnitinepalmitoyl transferase I and II) from biopsies of the vastus lateralis muscle at baseline and after 3 and 6 months. Muscle strength and strength endurance with surface EMG and macro EMG of the right knee extensors were also determined. The findings suggested a significant improvement in the intervention group in exercise capacity, particularly submaximal. The activity of PFK rose significantly, but that of the other enzymes did not when compared with the change in the controls. The continuous endurance exercise had no effect on the percentage distribution of slow-twitch and fast-twitch muscle fibres or on capillary density around these fibres in skeletal muscle. Also, the maximum voluntary force, strength endurance and the function of motor units remained unaffected.

LARSEN et al. (2002) also investigated the effect of a 3 month exercise training programme on skeletal muscle characteristics. Furthermore, they looked at the correlation of these muscle characteristics to cytokines and exercise capacity in CHF patients [112]. Skeletal muscle biopsies for enzyme-histochemical analysis were performed in 15 CHF patients with NYHA II-III (mean EF 33+/-5%) before and after a 12 week training period. The patients trained for 30 min, five times a week at 80% of the peak heart rate achieved at baseline ergometer cycle test. Also, 15 healthy men were used as controls.

The results proved in 5 patients significant muscle atrophy at baseline. Also, the percentage area of type I fibres (40.7+/-12.0 vs. 56.4+/-11.0%) and the thickness of type IIA (56.10+/-7.8 vs. 71.6+/-11.9 microm) and X-fibres (49.0+/-8.9 vs. 63.9+/-10.6 microm) were reduced, whereas the percentage area of type IIA fibres (52.1+/-13.3 vs. 36.4+/-9.9%) was increased in heart failure patients compared to healthy controls. There was a modest correlation between fibre thickness and the level of interleukin 6. After exercise training a reduction in

muscle area was found with a concomitant increase in interstitium. This reduction correlated to the improvements in the 6-min walk test (r=-0.558). The thickness of type IIX fibres increased (+5.6 microm) and the area of type I fibres decreased (-6.1%).

The authors therefore concluded that patients with CHF have a relatively increased area of type IIA fibres and a relatively decreased area of type I fibres compared to healthy individuals. The thickness of type IIA and type IIB fibres is decreased compared to normal individuals. A modest negative correlation between the level of interleukin 6 and fibre thickness at baseline, suggested that inflammatory cytokines may be involved in the pathogenesis of the CHF related myopathy. A significant correlation between the reduction of muscle area, with increased interstitum, and the increase in the 6-min walk test may indicate that the improvement is due to increased capillary density permitting better flow reserve to exercising muscles.

In a recent study GIELEN et al. (2012) assessed the age-dependent effects of a 4-week endurance training programme on the catabolic-anabolic balance in CHF patients – especially looking at muscle wasting aspects of the condition [113]. 60 CHF patients and 60 healthy controls were randomised to 4 weeks of supervised endurance training or to a control group. Before and after the intervention, vastus lateralis muscle biopsies were conducted. Thereafter, the expressions of cathepsin-L and the muscle-specific MuRF-1 were measured which are components of the ubiquitin-proteasome system involved in muscle proteolysis. At baseline, MuRF-1 expression was significantly higher in CHF patients versus healthy controls and after 4 weeks of exercise training, MuRF-1 mRNA expression was reduced by -32.8% in CHF patients aged ≤55 years and by -37.0% in CHF patients aged ≥65 years.

The results proved the catabolic state of CHF patients by showing an increased MuRF-1 expression in the skeletal muscle of these patients. Endurance training has positive effects on this state by reducing MuRF-1 levels.

Other types of endurance training include arm-cycling which is not commonly used in cardiac patients. However, it might offer an alternative and/or useful addition to the conventional treadmill and stationary bike. A study conducted not with CHF patients, but with hypertensive patients by WESTHOFF et al. (2008) found that regular upper limb aerobic exercise leads to a marked reduction in systolic and diastolic blood pressure and an improvement in small artery compliance [114]. It was therefore concluded that arm-cycling was a reasonable

option for hypertensive patients who want to support blood pressure control by exercise despite having coxarthrosis, gonarthrosis, or intermittent claudication.

Combining upper and lower body exercise has proven to be effective too when performed at the correct intensity. A study by AMOS et al. (1992) examined combined exercises and found that walking whilst using hand held weights generated oxygen consumption levels that were comparable with slow jogging [115]. The prescription for upper limb training intensity should ideally be based on an upper limb exercise test which is not always feasible. A study by FRANKLIN (1985) demonstrated that a lower maximal heart rate (11 beats/min mean) is generally the case when comparing upper and lower limb exercises [116]. A prescription for upper limb endurance exercise derived directly from a treadmill test may be inappropriately high. AACVPR (2006) therefore state that an upper limb prescription based on the heart rate for a lower limb prescription should be reduced by 10 beats/min and utilise RPE as an intensity modulator [117].

INTERVAL EXERCISE

The benefits of interval training in the context of CHF are the high workload that can be placed on the peripheral musculature without an accompanying increase in cardiovascular stress – and thereby causing positive muscular adaptations [118]. The Working Group on Cardiac Rehabilitation and Exercise Physiology and the Working Group on Heart Failure of the European Society of Cardiology (2001) proposed a protocol of 30s work at 50% of exercise capacity, followed by a 60s rest, repeated 10 times for a total of 15mins. A study by MEYER et al. (1997) reported an approximate 20% increase in ventilatory threshold and peak oxygen intake after 3 weeks of training, a similar improvement seen in cardiac patients completing up to 24 weeks of steady state training [118].

WILLENHEIMER et al. (1998) also investigated the effects of a four months interval training in CHF patients and concluded that this training method was safe and beneficial in heart failure patients up to the age of 75 years, especially in men with ischaemic aetiology. However, the effects of this training modality in women and patients with non-ischaemic aetiology should be further examined [119]. The authors included 49 CHF patients (intervention n = 22; controls n = 27) in the study. A supervised interval cycling training (90 second exercise and 30 second rest) for 15-45 minutes two days a week at 80% peak oxygen consumption or grade 15 Borg scale was conducted over a period of 4 months. Improvements vs. controls were found regarding maximal exercise capacity (6 +/- 12 vs. -4 +/- 12%)

and global quality-of-life (2 vs. 0 units), but not regarding maximal oxygen consumption or the dyspnoea-fatigue index. All of these four variables significantly improved in men with ischaemic aetiology compared with controls. However, none of these variables improved in women with ischaemic aetiology or in patients with non-ischaemic aetiology. The training response was independent of age, left ventricular systolic function, and maximal oxygen consumption.

NECHWATAL et al. (2002) conducted a three-week randomised trial comparing the improvement of functional capacity in CHF between continuous endurance training (EF 27.3%, n = 20) and interval training (EF 29.3%, n = 20) vs. a control group (EF = 26.6%, n = 10) [120]. VO_2 at the anaerobic threshold and at maximal exercise increased in the continuous exercise group by 13.7%. In the interval training group the increase was 14%. Continuous short-term exercise had no impact to central haemodynamics, whereas after interval training a significant increase at maximal exercise could be seen in the cardiac index and stroke volume with a drop in systemic peripheral resistance compared to the continuous mode. Interval training was further characterised by a higher short-term, but lower mean work load with a significantly smaller increase in lactate. Quality of life was improved according to the SF-36 questionnaire in both training groups but the psychological sum factor was three times as high, increasing to 24.2% in the continuous exercise group. It was therefore concluded that clinically stable patients with heart failure benefit from short-term endurance training. Both training modalities in this study seemed equally suited to improve functional capacity, but interval training leads to more pronounced improvement in haemodynamics compared to continuous endurance exercise, whereas the latter had a greater impact on psychological well-being and HRQL. Patients with heart failure and severe peripheral deconditioning tolerate higher workloads with more peripheral stress by using interval training. However, the study by Nechwatal et al. did not investigate the long-term effects of these different training modalities which could lead to further improvements of the functional status and possibly different results in HRQL.

PINA et al. (2003) formulated a statement document from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention following a meta-analysis of research in this area [121]. They reported that interval training at various intensities (50%, 70%, and 80% of maximal capacity) has shown to be beneficial to individuals with CHF but training intensity did not seem to directly influence the increase in exercise tolerance. They also stated that heart rate–derived exercise prescriptions may be inaccurate in patients with more advanced disease stages due to the chronotropic effect of β-blockers. This group also

reported that the ventilatory or anaerobic threshold generally occurs at a RPE of 13 to 15 and that RPEs of 12 to 13 were usually well tolerated by stable individuals. This document also stated that duration of exercise should include an adequate warm-up period (10 to 15 minutes) which may need to be longer in some patients. The exercise duration most frequently used was 20 to 30 minutes at the desired intensity and a cool-down period was also advised [121]. Most studies used 3 to 5 times per week as the optimal training frequency but individuals who develop exhaustion after training may need a day of rest between sessions although supplemental walking was generally encouraged on the non-training days.

Strength Exercise Interventions

In the past strength exercises for cardiac rehabilitation patients – especially the high risk group of CHF patients, was contraindicated. However, when performed at an appropriate level the evidence suggests that resistance training if adequately structured and dosed is safe, provokes fewer signs and symptoms of myocardial ischemia than aerobic testing and training, and results in notable increases in dynamic strength, peak exercise capacity, and submaximal endurance [122]. An important observation in an early study of DENNIS et al. (1988) was that even very low intensities of resistance training (20% of 1 RM) promoted notable increases in lifting capacity which promoted an earlier return to work in post MI patients [123]. Strength training in the rehabilitation of CHF patients is therefore likely to assume greater importance in the future.

Much research has been conducted over the years into the potential pros and cons of strength exercise within cardiac rehabilitation. MCCARTNEY (1999) deemed concerns raised regarding an excessive pressure response to be unwarranted as the incidence of ischaemia is less than that during dynamic exercises such as walking and cycling [124]. Major benefits from resistance training include improved muscular strength, increased peak exercise capacity and submaximal endurance, reduced ratings of perceived exertion during exercise and improved self-efficacy in strength-related tasks [125].

The question is, does the above also apply to the high risk group of heart failure patients? Generally the positive effects of strength training should especially benefit these patients with their catabolic state and the systemic component of CHF. These benefits in the context of cardiac rehabilitation are: improved posture and mobility – especially strength determined ADLs; improved venous return

from the extremities back to the myocardium ("muscle pump") and thereby supporting the cardiovascular function; muscle activity supports breathing, improved cardio vascular and hormonal function.

BJARNASON-WEHRENS et al. (2004) stated that when properly implemented by an experienced exercise therapist, supervised dynamic strength training programmes carries no inherent higher risk for the patient than aerobic endurance training [126]. They also reported that in selected individuals, as an adjunct to endurance training, resistance training can increase muscle strength and endurance, as well as positively influence cardiovascular risk factors, metabolism, cardiovascular function, psychosocial well-being and quality of life.

The importance of strength training for cardiac patients cannot only be justified by pointing at the long term effects on the cardiac condition, but the short-term benefits i.e. for heart transplant patients of which many have a history of chronic heart failure. A study conducted by BRAITH et al. (1998) proved a significant increase in muscle mass by a mean value of 4% above the baseline level in CHF patients who had received a heart transplant and were involved in a structured strength exercise regime as part of their rehabilitation programme (n=7), compared to a decrease in muscle mass of 7% six months post heart transplant surgery in a control group of the same population (n=7) [127]. See figure 9.

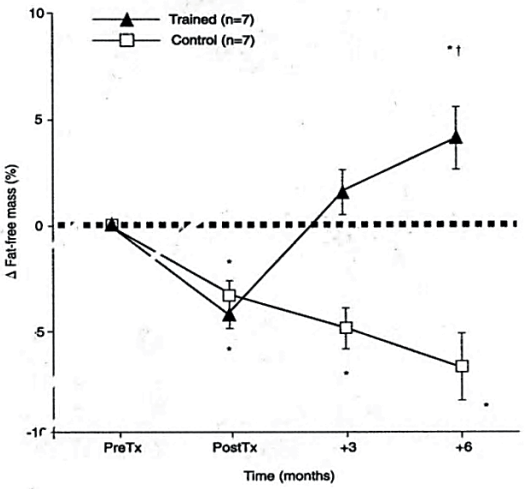

Figure 9: Strength training after cardiac transplantation: Effect on muscle mass (Braith et al. 1998).

Although there is some evidence of elevations in blood pressure being documented with high intensity strength training (80% to 100% of 1-RM performed to exhaustion), such elevations are generally not a concern during resistance training at a low- to moderate-intensity when performed with correct breathing technique which avoids the Valsalva manoeuvre [124]. There is in fact some evidence that suggests resistance training actually results in a more favourable balance in myocardial oxygen supply and demand than aerobic exercise because of the lower heart rate and higher myocardial (diastolic) perfusion pressure [128].

There are however other reports in cardiac rehabilitation regarding high intensity strength training, but these are concerning post MI rehabilitation rather than CHF patients. A study of ADAM et al. (2013) studied the effects of high-intensity, occupation-specific training (HIOST) in a series of firefighters during phase II cardiac rehabilitation [129]. The HIOST simulated firefighting tasks. No patient had to discontinue HIOST because of adverse arrhythmias or symptoms. For physicians who must make decisions about return to work, the authors recommend the information collected over multiple HIOST sessions might be more thorough and conclusive than the information gained during a single treadmill exercise stress and therefore should be considered.

A study by KARLSDOTTIR et al. (2002) investigated haemodynamic response during aerobic and resistance exercise in three groups of individuals (healthy, stable coronary heart disease and stable congestive heart failure) [130]. The rationale for the investigation was that there exists a potential for a high afterload to have a negative impact on left ventricular function which creates concerns for the safety of cardiac clients. Left ventricular function was measured during upright cycling (at 90% ventilator threshold) and one set of 10 rep leg press, shoulder press and biceps curl (at 60% to 70% of 1 repetition maximum) were performed. The study found that the pattern of changes in heart rate, blood pressure, LVEF, wall thickness and left ventricular internal diameter was similar across all three groups. There was however a marked difference in absolute values between groups. Even though there were elevations in diastolic and mean arterial pressures during resistance exercise, there was no evidence of significant rest-to-exercise deterioration in left ventricular function during leg press (EF in healthy subjects: 60%-59%, CAD: 56%-55%, CHF: 38%-37%), shoulder press (66%-65%, 59%-53%, and 38%-35%), or biceps curls (63%-58%, 53%-54%, and 35%-36%), as compared with cycle ergometry (63%-69%, 51%-57%, and 35%-42%). The study concluded that left ventricular function remains stable during medium-intensity strength exercises, even in patients with heart failure when performing

lower body resistance exercise, isolation upper limb work and overhead exercise - suggesting that these forms of exercise therapy can be used safely in rehabilitation programmes.

Another study of MANDIC et al. (2012) compared resistance versus aerobic exercise training in CHF and found that both aerobic and resistance training improve exercise capacity and may partially reverse some of the cardiac, vascular, and skeletal muscle abnormalities in individuals with CHF. Aerobic training has more beneficial effects on aerobic power (peak VO_2) and cardiac structure and function than resistance exercise training, while the latter is more effective for increasing muscle strength, endurance and promoting favourable arterial remodelling. Combined aerobic and resistance training should be the preferred exercise intervention to reverse or attenuate the loss of muscle mass and improve exercise and functional capacity, muscle strength, and quality of life in individuals with CHF [131].

As a result of these investigations there is now an acceptance of resistance training in the cardiac rehabilitation process, and it is endorsed by such notable agencies as the American College of Sports Medicine (AACVPR 2004; ACSM, 2010).

CIRCUIT STRENGTH TRAINING

In circuit training the sequencing of arm exercises, followed by leg work, with flexibility and co-ordination work following the more strenuous exercises enables clients to endure the session better and reduce the risk of local muscle ache and subsequent exercises cessation [132].

Although difficult to demonstrate consistently, one of the most important contributions of cardiac rehabilitation may be an improved sense of well-being and self-efficacy which translates into the measurable HRQL. EWART et al. (1989) was able to demonstrate in CAD patients that circuit training produced greater strength and endurance gains than volleyball, and these changes were accompanied by increased self-efficacy in the circuit training. The assertion that self-efficacy perceptions directly mediate involvement in challenging physical activities was supported by multiple regression analyses. These revealed that pre-training self-efficacy judgments predicted post-test strength gains even after controlling for baseline strength, type of training and frequency of participation in exercise sessions [133].

Another study by HAENNEL et al. (1991) which again was not conducted with CHF patients, but coronary artery bypass (CABS) patients looked into the effect of hydraulic circuit training (HCT) on stroke volume (SV), cardiac output (Qc), aerobic power (peak VO_2), and muscular strength and endurance in 24 patients. 16 patients were assigned randomly to 8 weeks of cycle training or HCT (n = 8 in each). Subjects assigned to cycle training exercised on bicycle ergometers. The HCT group exercised on a three-station circuit, completing three circuits per day. Each circuit consisted of three 20 s work intervals at each station with a 1:1 work to rest ratio. Results from the training groups were compared with results from eight patients who served as a non-exercising control group. Following training the peak VO_2 was significantly increased in the training groups (20% and 11% for the cycle and HCT groups, respectively). For both training groups, the increase in peak VO_2 was associated with increases in SV and Qc and a reduction in heart rate at submaximal levels of exercise. Only the HCT group demonstrated an increase in both muscular strength and endurance during knee and shoulder exercises. The authors of this study suggested that a circuit training programme can elicit improvements in cardiovascular fitness and muscular strength and endurance in cardiac patients [134].

Mixed Exercise Interventions

Mixed interventions in the treatment of heart failure patients are recently more often found – usually combining endurance exercise modalities with resistance training and potentially adding the benefits of both. This is common practice in any recreational and/or competitive training process and therefore seems a logical approach for CHF as well.

WIELENGA et al. (1999) investigated the effect of a mixed exercise intervention on quality of life in patients with chronic heart failure. 67 patients with mild to moderate CHF were randomised into an intervention and a control group. The intervention group conducted supervised cycling, walking, and ball games for 30 minutes, three days a week for eight weeks, then two days a week at 60% peak heart rate for a further 12 months. After the intervention a significantly larger decrease in *Feelings of Being Disabled* (a subscale of the Heart Patients Psychological Questionnaire) and a *significantly larger increase in the Self-Assessment of General Well-Being(SAGWB)* were observed in the training group. Exercise time and anaerobic threshold were increased in the training group only. The increase in exercise time was related to both Feelings of Being Disabled and SAGWB. It was concluded that supervised mixed exercise training improves both

quality of life and exercise capacity and can be safely performed by CHF patients [135].

MAIORANA at al. (2000) were able to demonstrate that a combined aerobic and resistance exercise training improves functional capacity and strength in CHF patients [136]. This study examined the effect of a circuit weight training programme on cardiorespiratory fitness, muscular strength, and body composition in 13 patients with CHF, using a prospective randomised crossover protocol. The 8-week training regime consisted of three, 1-h sessions of whole body exercise each week, concentrating on the large muscle groups of the lower limbs with selected torso and upper body exercises also included. Each of these sessions commenced and concluded with a 10-min warm-up or cool-down and stretching period. The conditioning phase of each session involved circuit weight training (CWT), a combination of cycle ergometry, treadmill walking, and resistance weight training. An exercise circuit consisted of seven resistance exercises alternated with eight aerobic exercise (cycling) stations. Each exercise was performed for 45s, with 15s intervals for the purpose of moving to the next station. To conclude the circuit, subjects spent 5 min walking on a treadmill. The active recovery (aerobic cycling) exercise between resistance stations was designed to maintain exercise HR within the training zone and to facilitate changes in cardiorespiratory fitness. Intensity and duration of the exercise programme were progressively increased throughout the programme. Initially, this was done by increasing the number of exercise circuits from one to three, followed by increasing the resistance or cycling load.

Peak exercise oxygen uptake increased significantly after the 8-week CWT programme (19.5 ±1.2 vs. 22.0 ±1.5 ml·kg21 ·min21), as did exercise test duration (15.2 ± 0.9 vs. 18.0 ±1.1 min). Submaximal exercise heart rate was significantly lower after training at 60 and 80W as was rate pressure product, whereas ventilatory threshold increased, from 52 ±3 to 58 ±3% of VO_{2peak}. The circuit training group also increased maximal isotonic voluntary contractile strength significantly.

LAOUTARIS et al. (2012) investigated whether a combined aerobic training with resistance training and inspiratory muscle training (IMT) could result in additional benefits over aerobic training alone in patients with heart failure [137]. 27 patients NYHA II/III were assigned to a 12-week aerobic training (n=14) or a combined aerobic, resistance and inspiratory muscle training (ARIS) (n=13). The aerobic training consisted of a bike ergometry at 70-80% of max heart rate. ARIS training consisted of aerobic training with a strength training of the quadriceps at 50% of

1 repetition maximum (1RM) and upper limb exercises using dumbbells of 1-2kg as well as IMT at 60% of sustained maximal inspiratory pressure.

The ARIS programme as compared to AT alone, resulted in an additional improvement in quadriceps muscle strength and strength endurance (50% 1RM×number of max repetitions), as well as maximal inspiratory pressure, exercise time, circulatory power (peak oxygen consumption × peak systolic blood pressure), reduced dyspnoea and increased HRQL.

Other Exercise Interventions

Selected occupational activities can also serve as useful upper body exercises as can other recreational or sports activities but caution should be exercised with cross country skiing with cardiac clients as heart rates are frequently inordinately high and do not correspond well with ratings of perceived exertion (RPE) [138].

SMART et al. (2011) reviewed the effects of various exercise modalities as well as respiratory muscle training and electrical stimulation on systemic inflammation CHF. The authors sought to determine whether physical therapy reduces serum levels of pro-inflammatory cytokines in heart failure patients. A total of 11 studies were included, with 4 reporting a post-training reduction in tumor necrosis factor α (TNF-α), of which 3 used traditional aerobic or resistance exercise and 1 used functional electrical stimulation. Reduced post-training serum levels of interleukin 6 were reported by one exercise study. The one study that employed combined resistance and aerobic training only showed soluble receptors TNF-α1 and TNF-α2 to be lower. The one study of respiratory muscle training and two studies that employed electrical stimulation had limited effect on cytokines and peak maximal oxygen uptake. With the exception of one study, those therapies that employed more than 5 sessions per week lowered serum TNF-α [139]. The review data suggests that physical therapies employing more than 5 sessions per week are most likely to reduce serum levels of TNF-α in CHF patients.

As a consequence of the above the therapy spectrum for CHF patients does not only need to be supplemented with updated evidence based guidelines for the rehabilitation phase III (Germany) and phase IV (UK) respectively in order to incorporate existing research in this area, but also a sufficient nationwide network of cardiac rehabilitation specialists in CHF to fill this health care gap for heart failure patients and translate evidence based rehabilitation methods into practice. Furthermore, dose-effect related long-term studies are needed to

identify the optimal frequency and duration of exercise interventions for CHF patients as well as recommendations for specific types of exercise and training relating to the severity stages of CHF (NYHA classes).

COPD

Since the beginnings in the early 1980's, respiratory rehabilitation has gained a wide acceptance in the scientific community. The development of objective health-related quality of life outcome measures and the demonstration of a physiological rationale for exercise training in patients with COPD have facilitated this acceptance [140].

Pulmonary rehabilitation is defined by the American Thoracic Society as *"a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise physical and social performance and autonomy"* [141].

The scientific evidence strongly supports pulmonary rehabilitation as part of the spectrum of management for patients with COPD. The effects of a long-term exercise therapy for COPD patients result in clinically and statistically significant improvements in important domains of HRQL, including dyspnoea, fatigue emotional function and mastery. When compared with the treatment effect of other important modalities of care for patients with COPD such as inhaled bronchodilators or oral theophylline, rehabilitation resulted in greater improvements in important domains of HRQL and functional exercise capacity [142,143,144].

Pulmonary rehabilitation should be considered for patients with COPD who have dyspnoea or other respiratory symptoms, reduced exercise tolerance, a restriction in activities because of their disease, or impaired health status [145]. According to the American Thoracic Society (ATS) there are no specific pulmonary function inclusion criteria that indicate the need for pulmonary rehabilitation, since symptoms and functional limitations direct the need for pulmonary rehabilitation [146] – especially as much of the morbidity in COPD results from secondary conditions which are often treatable such as peripheral muscle dysfunction, anxiety and loss of body mass [147]. The pulmonary rehabilitation programme should be a holistic approach, including exercise training, education, psychosocial/behavioural intervention, nutritional therapy, outcome assessment and promotion of long-term adherence to the rehabilitation recommendations.

Few investigators have examined the long-term benefits of rehabilitation [149] and exploration of strategies to maintain the early benefits [148,149]. As the care of patients with COPD is largely symptomatic [150], quality of life should be considered as the primary outcome in pulmonary rehabilitation. The evidence is very strong, showing that pulmonary rehabilitation is effective in relieving dyspnoea and fatigue, and in improving patients' emotional function and control over the disease.

Identifying the ideal method of exercising patients during pulmonary rehabilitation has been much debated. The evidence is unequivocal that exercise is an important part of pulmonary rehabilitation; however the merits of certain methods over others are yet to be established. There have been many trials and interesting findings but further research is required. This section will discuss the current research behind exercise prescription for pulmonary patients.

Guidelines

Clinical practice guidelines must however consider that pulmonary rehabilitation is often unavailable. For instance, in Canada, a national survey conducted in 1999 indicated that less than 2% of the population with COPD per annum has access to such. The situation in Germany is similar - 850 pulmonary rehabilitation groups compared to over 6000 cardiac rehab groups – especially as the conventional pulmonary rehab groups' focus their efforts on asthma rather than COPD. Thus, there is not only need for additional research proving the long-term effects of pulmonary rehabilitation in COPD relating to severity stages and specific exercise modalities, but there is more so an urging necessity to implement specialised COPD exercise programmes and groups respectively in conjunction with specific exercise focused disease management programmes (DMP) that will give COPD patients the opportunity to participate in long term pulmonary rehabilitation programmes in their community – conducted by qualified exercise professionals.

The ACSM (2010) recommends that individuals with mild pulmonary disease and well controlled asthma should perform either continuous or intermittent physical activity at least 3-5 times per week for 20-30 minutes [151]. The ACSM guidelines also state that at present there are no optimal exercise intensities for this population, but they do recommend that exercise should be performed at an intensity that was equivalent to that of healthy older adults. On a scale of 0-10 for physical exertion, intensity should be between moderate (5-6) and vigorous (7-8) [153].

Resistance training is considered to be an integral part of pulmonary rehabilitation programmes. ACSM (2010) guidelines state that individuals with mild pulmonary disease and well controlled asthma may exercise following the exercise prescription guidelines for strength training laid out for healthy adults. It is also recommended that each major muscle group should be trained 2-3 times per week on non-consecutive days. Each exercise should utilise 2-4 sets for 8-12 repetitions with volitional fatigue occurring close to or at 12 repetitions.

The guidelines released by the German Society for Pneumology and Respiratory Medicine in conjunction with the German Society for Rehabilitation Science are closely related to the AACVPR and BTS guidelines [152]. They recommend muscle hypertrophy training and/or strength endurance training of the lower limbs and upper limbs as well as cardiorespiratory endurance training with reference to AACVPR and BTS respectively (evidence level A). The guidelines also state that endurance exercises can be conducted with or without monitoring. Interestingly strength training is firstly named in the order of interventions. Coordination exercises are also mentioned, but without any evidence level or reference. Training of respiratory muscles is also recommended as breathing exercises or inspiratory muscle training (IMT) as part of these guidelines – referring to AWL/DGP ACCP/AACVPR. According to the German guidelines ADL–training can be considered as an additional, but it is mentioned that ADL-Training only has a level of evidence D [152].

Meta-Analysis

A systematic review of evidence into exercise and COPD was conducted by RIES et al. (2007) and from this work the Joint ACCP/AACVPR Evidence-Based Guidelines: Intensity of Aerobic Exercise Training was developed [153]. The purpose of these guidelines was to update existing knowledge and inform working practices in pulmonary rehabilitation.

The review concluded that lower-extremity exercise training at higher exercise intensity produces greater physiological benefits than lower-intensity training in patients with COPD and that both low and high intensity exercise training produce clinical benefits for patients with COPD [153].

Endurance Exercise Interventions

Aerobic training is still considered to be the main non-pharmacological treatment and therefore one of the key components in the rehabilitation of COPD. This view however has been challenged in recent years. Similar to the endurance exercise modalities in CHF, the two effective strategies for creating progression within

exercise prescription have been reported – either setting a duration of continuous exercise and then increasing work rate i.e. intensity or setting the intensity then increasing the duration [154,155,156].

CONTINUOUS EXERCISES

BERNARD et al. (1999) compared aerobic training to a combination of aerobic and resistance training in COPD patients and concluded that the addition of strength training to aerobic training in patients with COPD was associated with significantly greater increases in muscle strength and mass, but does not provide additional improvement in exercise capacity or quality of life [157]. This is however debatable. Because of the systemic nature of many COPD symptoms – again similarities to CHF occur, higher exercise intensities have been applied in pulmonary rehabilitation in recent years. Table 9 summarises the results of three studies by VOGIATZIS et al. (2002) [158], ROOYACKERS et al. (2003) [159] and O'DONNEL et al. (1998) [160] who investigated the effects of higher training intensities in the context of rehabilitation modalities in COPD.

Table 9: Key outcomes concerning the application of high intensity exercises in COPD patients.

High Intensity training vs. Low Intensity training
Greater training effects after high intensity exercise (dose response).
Longer endurance ability after high intensity training.
Reduction in blood lactate levels post exercise with high intensity training.
Improved Quality Of Life (QOL) scores with high intensity exercise.
Reduction in reported disease linked symptoms with low intensity training.

INTERVAL EXERCISES

A study by VOGIATZIS et al. (2005) that was included in the above review produced the following results when comparing high intensity interval training in COPD patients to the continuous method: interval training significantly increases peak oxygen uptake, produces lower lactate levels at a sub maximal workload and significantly less dyspnoea and leg discomfort when compared to continuous work [161].

A systematic review conducted by BEAUCHAMP et al. (2010) compared the effects of interval versus continuous training on peak oxygen uptake, peak power, 6 minute walk test distance and health-related quality of life index in individuals with COPD. They concluded that interval and continuous training did not differ in their effect on measures of exercise capacity or health related quality of life and that interval training may be considered as an alternative to continuous training in patients with varying degrees of COPD severity [162].

KORTIANOU and colleagues (2010) also reviewed the effectiveness of interval training in COPD patients [163] and derived concrete practical recommendations from this. The work group stated that in healthy elderly individuals and CHF patients there is evidence that interval training is superior to continuous exercise in terms of physiological training effects, but in patients with COPD, there is not such evidence. Nevertheless, application of interval training in this population has been shown to be equally effective to continuous exercise as it induces equivalent physiological training effects but with less symptoms of dyspnoea and leg discomfort during training [163].

KORTEIANO et al. furthermore state interval training has shown to allow lower limb exercise to be sustained at a high intensity which otherwise would not be tolerable which is especially applicable to patients with advanced COPD, who are unable to sustain exercise intensities sufficiently long enough to obtain a physiological training effect because of ventilatory limitation [163]. This review also found that *"… these patients can endure high-intensity interval training in a rehabilitation setting for long periods of time with lower symptoms of dyspnoea and leg discomfort compared to the conventionally implemented continuous training"* [163].

This workgroup also point out that BEAUCHAMP et al. [162] in their recent systematic review of 8 randomised control trials (388 patients) failed to reveal the efficacy of interval training over that of continuous in terms of enhancing exercise tolerance and quality of life in patients with severe COPD. The authors presented some limitations (training protocols heterogeneity, small sample sizes), suggesting that further research is needed in order to reveal the superiority of interval training in severe COPD [163].

The main criticism of KORTEIANO et al. is that issues such as performing comparisons among training groups exercising at different total work-loads during the course of rehabilitation, were not fully addressed in previous studies, but need to be clarified by future research. However, in support of the above argument there are studies in patients with CHF and healthy elderly age-matched

individuals (MORRIS N et al., 2003; AHMAIDI S et al., 1998) advocating the superiority of high-intensity interval training in terms of improvement in aerobic capacity, cardiac hypertrophy, left ventricular systolic performance, and antioxidative status [163].

The authors concluded after their review that *"… interval training in severely disabled COPD patients is associated with stable metabolic demands, low minute ventilation and rates of dynamic hyperinflation, and increased total exercise duration than that of constant-load exercise. Hence, the application of this method in the rehabilitation setting has the potential to convey important clinical benefits, as it allows the application of intense loads on peripheral muscles for sufficiently long periods of time*" [163].

Interval exercise therefore provides a good alternative to continuous exercise training in order to improve compliance with exercise and the effectiveness of this treatment. However, the authors also propose that studies are required to determine the efficacy of interval exercise training in long-term follow up and on adherence in pulmonary rehabilitation programmes [163].

Regarding practical recommendations concluded from this review, the following key components were identified – see table 10.

Table 10: Recommendations for an effective interval training in the treatment of COPD by KORTEIANO et al. (2010) [163].

Practical Recommendations for Interval Exercise
• Frequency: 3-4 times weekly.
• Interval mode: 30 seconds exercise period with 30 seconds rest or even 20 seconds exercise – 40 seconds rest.
• Intensity and duration: initially familiarize the patients on the cycle ergometer at an intensity equivalent to 80% of the maximal work load for 15 to 20 minutes for the first 3 to 4 sessions. The Borg Scale of perceived exertion can be used to more easily monitor exercise intensity. Increase training work load by 5% to10% of peak capacity when patients rate their perceived dyspnoea as moderate. If the 10-point Borg scale is used to describe exercise intensity, most exercise should be performed between 5 to 6 intensity for the legs and 3 to 4 for dyspnoea.
• Increase total exercise time from 30 to 90 minutes per session (including

rest periods), at intensities that progressively reach 150% of the baseline maximum work load.

• Suggest pursed-lip breathing during rest periods to increase tidal volume and reduce breathing frequency.

• Teach patients to perform all daily activities (e.g., stair climbing, uphill walking) at an interval mode consisting of short bouts of activity lasting 10 to 15 sec and rest periods of 15 sec.
• Give written instructions to the patients for home practice.

Strength Exercise Interventions

RIES et al. (2007) found that the addition of a strength training component to a programme of pulmonary rehabilitation increases muscle strength and muscle mass which can improve HRQL and the ability to deal with activities of daily living (ADL) in COPD patients [153].

PHILLIPS et al. (2007) stated that a single set of resistance training can elicit significant improvements in both strength and functional fitness, which is not obtained by traditional pulmonary rehabilitation alone. The researchers concluded that the findings may have important implications for programme design, application, and adherence in pulmonary rehabilitation [164]. Although most other research shows that resistance training has little effect upon lung functioning such as FEV_1.

SEMPLE and MCKUNE (2007) however, suggest that although FEV_1 is important in the diagnosis of COPD, it cannot be reliably correlated with exercise capacity, dyspnoea or HRQL. They propose that the lack of improvements in pulmonary function parameters following resistance training interventions may not be that clinically significant [165].

It has also been suggested that resistance training may be better tolerated due to the intermittent nature. However, concrete recommendations regarding the intensity, duration and frequency of resistance training in this population only recently started to emerge. However, there is still a significant knowledge gap for exercise intensities, durations etc. differentiated by severity stages in COPD.

According to a publication by NELSON et al. (2007) exercises should be performed at 60-80% of the 1RM, a resistance training session in a pulmonary rehabilitation

setting should include 8-10 exercises involving the major muscle groups in bouts of 8-15 repetitions for at least 30 minutes on two or three non-consecutive days each week [166]. Multiple sets of repetitions (2-5 sets) provide greater benefit according to LANGER et al. (2009) [167]. O'SHEA et al. (2004) state that because of the circumstance that muscle weakness is a common problem in this population and progressive resistance exercise represents a beneficial treatment for improvements in muscle strength. Moreover, improvements in muscle strength can be obtained when progressive resistance exercise is conducted alone or in combination with aerobic training and therefore produce synergy effects in conjunction with other training types during pulmonary rehabilitation [168].

Mixed Exercise Interventions

VOGIATZIS (2011) developed strategies of muscle training in very severe COPD patients (GOLD III and IV) that in patients with profound muscle weakness and intense breathlessness upon physical exertion, execution of short bouts of interval or local muscle strength conditioning, along with oxygen substitution constitutes a feasible and effective pulmonary rehabilitation approach [169].

REIS et al. (2013) investigated the long-term effects of a mixed pulmonary rehabilitation programme in order to determine the effects on exercise tolerance, dyspnoea, haemodynamic variables and quality of life [170]. A convenience sample of 36 COPD patients was therefore enrolled and underwent a 24 months long exercise intervention consisting of aerobic training, upper-limb exercises and inspiratory muscle training (IMT). The results showed a significant improvement in haemodynamics, demonstrated by the gradual reduction in heart rate, blood pressure and MvO_2 (double product) which showed after the first year. The lipid profile showed a reduction of low density lipids and an increase of the high density lipids levels starting from the 6th month. Exercise tolerance, dyspnoea, respiratory muscle strength and HRQL also improved during the same period. The authors therefore concluded that a 24-month pulmonary rehabilitation programme comprising of a mixed exercise intervention consisting of strength training, endurance exercises and IMT leads to a progressive improvement in the aforementioned metabolic, cardiorespiratory and functional fitness parameters making a significant difference to the quality of life in COPD patients [170].

Other Exercise Interventions

Expiratory flow limitation promotes dynamic hyperinflation during exercise in COPD patients with a consequent reduction in inspiratory capacity. This aspect is

limiting their exercise tolerance. Therefore, the exercise capacity of COPD patients with tidal expiratory flow limitation at rest depend on the magnitude of inspiratory capacity [171].

A study by DIAZ et al. (2000) investigated the role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest [171]. 52 patients were included in the study. Negative expiratory pressure uptake was measured during an incremental symptom-limited cycle exercise. A close relationship of the maximal work rate and VO_{2max} to inspiratory capacity was found (r=0.73 and 0.75). In the whole group, stepwise regression analysis selected inspiratory capacity and FEV_1, forced vital capacity (% predicted) as the only significant contributors to exercise tolerance. The detection of flow limitation therefore provides useful information on the factors that influence exercise capacity in COPD patients [171]. Accordingly, in patients with flow limitation, inspiratory capacity appears as the best predictor of exercise tolerance, reflecting the presence of dynamic hyperinflation which in return explains why inspiratory muscle training should be beneficial in the treatment of COPD as an additional type of exercise therapy.

The first interest in inspiratory muscle training (IMT) as part of the rehabilitation of COPD patients emerged after LEITH and BRADELY (1976) demonstrated an increase in inspiratory muscle function by applying a specific inspiratory muscles training in healthy individuals [172]. To date, several randomised controlled studies examined the effect of IMT in the treatment of COPD. Hence, there appears to be strong evidence that IMT, if adequately prescribed yields significant improvements in relevant parameters in COPD patients.

GOSSELING and colleagues (2011) conducted a meta-analysis looking at the impact of inspiratory muscle training in patients with COPD, which included 32 randomised controlled trials on the effects of inspiratory muscle training (IMT) in COPD patients [173]. The analysis proved significant improvements in maximal inspiratory muscle strength (PI_{max} +13 cmH2O), endurance time (+261 s), 6- or 12-min walking distance (+32 and +85 m respectively) and HRQL (+3.8 units). Dyspnoea was significantly reduced (Borg score -0.9 point; Transitional Dyspnoea Index +2.8 units) and endurance exercise performance tended to improve, while no effects on maximal exercise capacity were found. However, respiratory muscle endurance training revealed no significant effect on PI_{max}, functional exercise capacity and dyspnoea [173]. The authors concluded that the addition of IMT to a general exercise training programme improves PI_{max} and tends to improve exercise performance and therefore can be understood as a useful add on tool for the rehabilitation of COPD patients.

Summary of the physiological Effects of Rehabilitation in CHF and COPD

Cardiopulmonary rehabilitation is recognised as a core component of the disease management of patients with CHF and/or COPD which is designed to improve their physical and psychosocial condition. The scientific evidence increasingly leads to belief that the main effects of cardiopulmonary rehabilitative exercise training are focused on skeletal muscles that are regarded as dysfunctional in both conditions VOGIATZIS (2013) [174]. This is explicitly referring to the important peripheral muscular adaptations in both disease entities after completing a rehabilitative exercise training programme, namely - increased capillary density, blood flow, mitochondrial volume density, fibre size, distribution of slow twitch fibres, and decreased lactic acidosis and vascular resistance [139]. Decreased lactic acidosis at sub-maximal exercise levels not only offsets the occurrence of peripheral muscle fatigue and muscle discomfort, but also concurrently mitigates the additional strain on the respiratory muscles caused by the increased respiratory drive, thereby reducing dyspnoea sensations [174]. Furthermore in patients with COPD, exercise training reduces the degree of dynamic lung hyperinflation leading to improved arterial oxygen and central hemodynamic responses, thus increasing muscle oxygen availability. In patients with CHF, exercise training has beneficial sympathoinhibitory effects, as well as favourable effects on normalisation of neurohormonal excitation [174].

The physiological benefits above apply to COPD and CHF patients generally - independent of the disease severity and are directly associated with improved exercise tolerance, functional capacity and quality of life.

3 CHF STUDY

Effects of Non-Pharmacological Interventions on Health Relevant Parameters in Chronic Heart Failure Patients.

3.1 Objectives

The non-cardiac factors in Chronic Heart Failure (CHF) such as neurohormonal changes, muscle atrophy and others, independently, can cause dyspnoea, fatigue, and oedema that are characteristic of the clinical syndrome of congestive heart failure [175,176]. The treatment of heart failure therefore involves counteracting two related but largely independent processes.

A key role in this context plays the so called vicious cycle of heart failure, which is mainly characterised by an increase of symptoms during physical activity, therefore the patient avoids physical activity and this initiates deconditioning processes which lead to a further loss of functional capacity on all levels, including skeletal muscle mass, catabolic hormonal changes and an increase of cardiac specific symptoms [177,178,179,180].

Traditionally patients have been recommended to avoid physical exercise, because it was believed that the strain might aggravate the cardiac condition and therefore is harmful. This belief has been proved wrong in the last two decades and several studies demonstrated the positive effects of exercise training in CHF patients [181,182,183,184,185,186]. Most studies used an endurance training intervention. However, more studies emerged more recently that investigated the effects of strength training exercises [187,188,189].

Thus the aim of this study was to examine the different effects of an endurance training using the continuous training principle, a high intensity strength training and a circuit training vs. a dietary comparison group (non-exercising group) in an outpatient setting on cardiac specific parameters: ejection fraction (EF), left ventricular end diastolic diameter (LVEDD), NYHA classification and NT-pro-BNP as well as exercise specific parameters using the peak oxygen uptake (VO_{2peak}). These groups were also compared against a control in some of the aforementioned parameters and also hospitalisation rate and mortality.

Therefore, the following hypotheses were investigated:

1. The hospitalisation rate of CHF patients can be reduced by different exercise modalities.
2. Mortality rate can be reduced in CHF patients by exercise interventions.
3. Strength training interventions are safe to be used in CHF patients applying high intensities and longer durations.
4. Cardiac specific parameters can be improved by structured exercise interventions.
5. The strength performance of CHF patients can be improved significantly by using strength exercises.
6. The endurance performance can be improved by applying different exercise modalities.

3.2 Methods

3.2.1 Subjects

A total of 125 CHF patients (NYHA II-III) were recruited from various cardiac practices in the area of Dortmund (Germany) and a collaborating hospital in Dortmund (Bethanien hospital). They were randomised by the project manager using the Excel random number function without having any medical background information on the patients and divided into three intervention groups, a comparison group (dietary intervention and education, but no exercise training) and a control group. 78 patients of the intervention groups and comparison group completed the study (Table 11). The control group was only created for the purpose of reference values for mortality and hospitalisation with standard medical interventions and did not undergo any of the other testing. The control group consisted of an additional 25 patients of whom only 18 completed the study due to mortality. Thus, mortality and hospitalisation data therefore refers to n= 105 patients and n= 96 patients respectively. A minimum number of 20 patients per group were considered to be sufficient for a statistical analysis by a bio statistician (Westphalian Wilhelms University, Munster, Germany).

The gender distribution of the intervention and comparison cohort consisted of 76.6% men and 23.4% women. 63.6% of the patients were diagnosed with CHD, 23.4% were presented with Diabetes Mellitus and 16.9% showed atrial fibrillation. There was no significant difference in the medication scheme between all groups.

In the following the medication specifications of the cohort are presented: beta-adrenergic blocking agents: 94.8%, ACE inhibitors: 97.4%, diuretics: 89.6%, Digitalis: 32.5%, aldosterone antagonists: 36.4% and lipid-lowering agents: 62.3%. 11.7% of the patients had a defibrillator.

Table 11: Specifications of the patients who completed the study in the intervention and comparison group (n=78) - not the control group.

Age (years)	67.5 ± 9.4
Height (cm)	173.3 ± 9.5
Weight (kg)	81.8 ± 15.6
Body Mass Index (kg/m^2)	27.1 ± 3.9
NYHA-classification	2.6 ± 0.5
EF (%)	30.7 ± 7.0

Declaration of Consent:

All subjects had to sign a declaration of consent before being considered for one of the study groups. The patients received information in writing about the overall study design, the specific intervention and benefits and risks associated with it. Furthermore, a personal interview was held by a physician. The study was approved by the Ethics Committee of the Westphalian Wilhelms University, Munster (Germany).

Study Termination:

Every patient could terminate the study at any time.

Inclusion Criteria:

- $\geq$ 18 years
- Women and men
- Dilative cardiomyopathy with limited systolic LV-Function
- Clinical class NYHA II and III [Pilot study: IV – with age limitation]
- Genesis: ischemic and non-ischemic
- EF $\leq$ 40 %
- Stabile cardiac condition for the last 6 weeks

- Optimised drug therapy
- Rhythm therapy completed (ICD implantation or already initiated CRT-therapy)
- All invasive therapy options were used
- Co-morbidity such as diabetes mellitus, orthopaedic problems, atrial fibrillation or COLD (GOULD class I-III) was possible
- The patient's declaration of consent to participate in the study

Exclusion Criteria:

- Medication scheme (titration phase) with ACE-inhibitors/Beta-blocker still to be completed
- Malign, current arrhythmia therapy
- Comorbidity: unstable insulin dependent diabetes mellitus, COLD (GOULD class IV), acute orthopaedic problems

The presented results are referring to the 78 subjects who completed the study. The total of 22 drop outs were distributed across the four groups as follows: Endurance Training Group (ETG): 3 personal reasons, 1 hospitalisation; Strength Training Group (STG): 3 hospitalisation, 2 personal reasons; Circuit Training Group (CTG): 2 hospitalisation, 2 personal reasons, 1 death; Comparison Group (CPG): 1 moving house, 1 death, 1 no interest, 1 personal reasons, 4 hospitalisation.

3.2.2 Experimental Procedures

Study Design

TEST PROCEDURES

The test profile was applied at three points (every three months). Two weeks were allocated for the data collection.

The test profile of the baseline, the interim and the final re-test included the following procedures: clinical examination by a cardiologist including a resting ECG (data not presented), Trans-thoracic echocardiography, NT-pro-BNP, a cycle ergometry with spirometry and strength testing (12-RM).

INTERVENTIONS

The exercise intervention of each group was divided into two phases of three months each (Fig. 10). In the first four weeks the patients underwent two therapy sessions a week, which then increased to three sessions a week in an outpatient rehabilitation setting, which was attached to a specialised practice for cardiology. The patients were examined by a cardiac nurse before every intervention in the first three months and then once a week in the second three months.

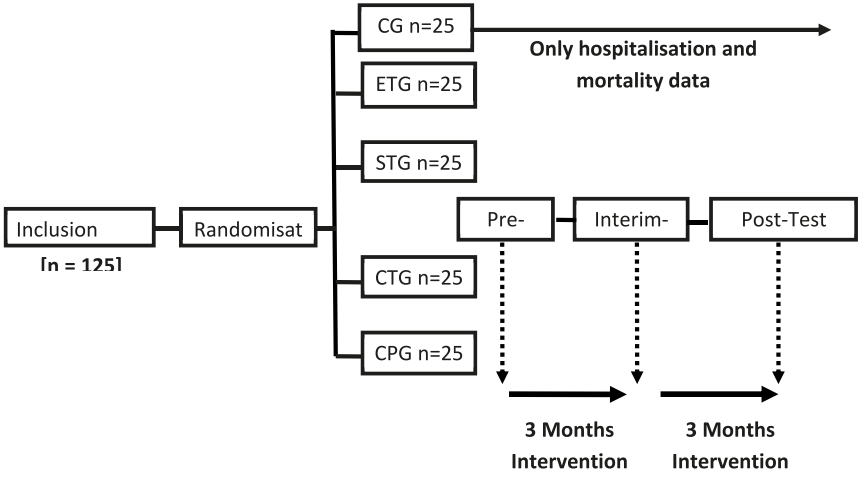

Figure 10: Schematic Study Design

Endurance Training Group (ETG)

The patients trained at the beginning according to the *repetition principle* during which they had two to three individual work intervals on the cycle ergometer and almost complete resting periods in-between. The overall exercise duration was between 15 and 30 minutes depending on the individual fitness, excluding breaks.

After the first four weeks the conventional *continuous principle* was applied. This phase was characterised by an extensive work profile. In the second intervention phase the *variable continuous method* was used to utilise further physiological adaptation reserves and to motivate the patients. In the final stage of this phase the *conventional continuous method* was applied again on a higher level to create a new physiological stimulus (see table 12).

Figure 11: Supervision training

Figure 12: Endurance and strength groups, exercising parallel

Strength Training Group (STG)

This training was based on an increase of maximal strength by an enlargement of the muscle diameter. After the initial anatomical adaptation phase, higher intensities with less repetitions and higher numbers of sets were applied. Large muscle groups and complex exercises which are more relevant for activities of daily living (ADL) were included. In the second intervention phase a *Pyramid Training* was applied to give a new physiological stimulus followed by a so called *Antagonist Training,* which is characterised by slightly shorter breaks, but is also considered to be a type of hypertrophic strength training (table 12).

Figure 13: Training with electro-pneumatic strength training devices.

Circuit Training Group (CTG)

The work profile of this intervention was characterised by an alternating change of exercises that train different muscle groups in a certain order with a work duration that slowly increases from 30 seconds to 75 seconds and a break duration of just 30 seconds. This specific series of exercises otherwise known as *Circuit* was absolved initially once and eventually increased to up to three circuits.

On this basis the exercises changed in the second intervention phase including a five minute cycle ergometer exercise after every three strength exercises (see table 12).

Comparison Group (CPG)

This group was a non-training group. The patients of the CPG only attended weekly seminars for 60 to 90 minutes where theoretical background knowledge was delivered about the disease, the medication and dietary recommendations as well as practical cooking sessions in regular intervals. This intervention was in adherence with the disease management guidelines of the European Society of Cardiology. No exercise intervention was applied and the physical activity levels of the patients were monitored to avoid any life style changes.

Figure 14: Information class for patients and dietary class in the educational kitchen.

Control Group (CG)

The control group consisted of originally 25 CHF patients who met the same inclusion and exclusion criteria, but only underwent the standard clinical testing in the local hospital and received no other specific intervention. Thus, it can be assumed that there was no lifestyle change. This group only functioned as a reference cohort for hospitalisation and mortality data and therefore does not appear in any other data. The dropout rate in the control group was n= 7 due to mortality.

Table 12: Intervention Scheme.

Intervention Group	***Intervention Method***	***Intervention Duration***	***Intervention Details***
Endurance Training Group (ETG)	*1.Repetition principle*	4 weeks	The patients had two to three individual work intervals on the cycle ergometer and almost complete resting periods in-between. The Effective work duration of 15-30 minutes at an intensity of 70-80% of the peak performance achieved in the incremental test.
	2.Conventional Continuous Method	8 weeks	Increasing the exercise duration up to 40 minutes followed by a slight increase in intensity.
	3.Variable Continuous Method	6 weeks	A variable work profile was applied that is characterised by a four minute workload at a low intensity (65-70% of the maximal performance in the interim test) and a higher workload for two minutes (80-85%). This profile changed every two weeks firstly to three minutes at a higher workload and then four minutes.
	4.Conventional Continuous Method	6 weeks	Slow increase of the work duration up to 45 minutes, followed by an increase in intensity.
Strength Training Group (STG)	*1.Anatomical Adaptation Training*	4 weeks	Intensity: sub-max. (50-60% of the 12RM), Reps: 15-20, Sets:2-3, Pause:1 min.
	2.Hypertrophic Training	8 weeks	Intensity: maximal, Reps: 12/10-8, Sets: 2-3, Pause: 2 min.
	3.Pyramid Training	6 weeks	Intensity: max. (60,100,110% of the interim 12RM), Reps: 20-12-8, Sets: 3, Pause: 2 min.
	4.Antagonist Training	6 weeks	Intensity: maximal, Reps: 12-10, Sets: 2-3, Pause: 1 min.

Intervention Group	*Intervention Method*	*Intervention Duration*	*Intervention Details*
Circuit Training Group (CTG)	*1.Basic-Circuit*	12 weeks	The exercise duration was extended by 15 seconds every four weeks from 30 seconds to 45 and then 60 seconds. The number of circuits increased with the duration of the training. Duration: 30-60s/exercise, Intensity: sub-max (60-70% of the 12RM), Sets:1-3, Break: 30 s.
	2.Advanced-Circuit	12 weeks	This method was characterised by a systematic change of strength and endurance exercises. The patients cycled for five minutes at an intensity of 60-70% $Watt_{max}$ after every three strength exercises. Duration: 60-75 s/exercise, Intensity: sub-max., Sets: 2-3, Pause: 30 s.

EQUIPMENT

Spirography

In order to evaluate spirometric parameters the open system spirometer $K4b^2$ of the company Cosmed (Rome, Italy) was used. This system uses a volume-sensor (Triple-V-Sensor). The Triple-V-Sensor sends digital volume impulses to the Oxycon. Using an infrared analyser and a paramagnetic sensor the CO_2 and O_2 concentration were measured respectively.

Cycle Ergometry

The cycle ergometer 1500 of the company Ergoline (Munich, Germany) uses magnet technology to build up a resistance, which can be varied in one Watt steps. The electronic display showed the performance, the time, rpm and the heart rate.

Echocardiography

The Hewlett Packard Sono 2 5500 (Andover, Massachusetts, USA) was used for the echocardiography data collection. This 3D echocardiography acquisition technology is based on the automatic serial collection of 2D ultra-sound cross-sectional images.

Cardiac Measurement Analysis

All cardiac sonographic images and raw data were blinded and cross analysed and/or measured in the case of LVEDD and EF by an independent cardiologist. Only this cardiac data was used for further analysis and is presented in the result section.

Blood Pressure Device

Blood pressure (BP) during the strength training intervention was measured using the FINAPRES 2300 which is a non-invasive BP measurement device. The FINAPRES uses the volume-compensation-method with a photoplethysmograph imbedded in a miniature blood pressure cuff that is strapped to a finger and thereby measures the intra-arterial pressure by an indirect method.

Strength Training Devices

The strength training equipment of the company HUR (Kokkola, Finland) works with electro-pneumatic technology, which enables the user to build up a resistance in 1kg steps. The resistance shown in kg on the display equals the produced force in N, which made it possible to use the equipment as training as well as diagnostic devices.

3.2.3 Statistics

The missing data of some individuals, who could not attend one of the tests, was replaced by the missing value procedure using the group mean value. The data are expressed as mean $\pm$ SD. In order to identify differences between the various measurement points in each group, the one way *Anova* with repeated measurements was used. The one way *Anova* without repeated measurements was applied to show the differences in percentages between pre and post-test points. The *Duncan* test was used as a post hoc test. The *Multiple Regression Analysis* was carried out to analyse the relationship between the different variables. P-values < 0.05 were considered significant. The data was analysed

according to the *Per-Protocol* procedure. The survival data was calculated using the *Kaplan-Meyer model*.

3.3 Results

The NT-pro-BNP [pg ml^{-1}] only showed a significant difference in the ETG between post vs. pre ($p<0.01$) and the CPG between interim vs. pre ($p<0.05$) (Table 3). The ejection fraction (EF) increased significantly in all training groups at all test points, but no significant change in the CPG was demonstrated. The LVEDD behaved in the same way. The ETG showed a relative increase of 50% ($p<0.05$ vs. CPG) and the CTG with 66% and the STG with 61% (both $p<0.01$ vs. CPG) (Table 13). Finally the peak VO_2 showed no significant changes in the CPG, but again significant changes in all the training groups. Especially the STG showed the greatest increase from 15 to 22 ml min^{-1} kg^{-1} (Table. 13).

Overview of cardiac and cardiorespiratory data

All exercise groups showed a significant increase in the EF compared to the CPG, which had an improvement of just 11%. The ETG showed an increase of 50% ($p<0.05$ vs. CPG) and the CTG with 66% and the STG with 61% (both $p<0.01$ vs. CPG).

Table 13: Results of the Cardiac and the Exercise Tests.

		ETG	CTG	STG	CPG
NT-pro-BNP [pg ml^{-1}]	pre	1495±1555	2115±1880	1333±1498	1557±907
	mid	1262±1134	1704±1592	1121±1607	1105±733 [b]
	post	934±702 [a]	1602±1772	1078±1351	1248±794
EF [%]	pre	31±6	29±7	30±7	33±8
	mid	41±9 [d]	40±7 [d]	39±8 [d]	36±8
	post	46±8 [a,c]	45±11 [a,e]	45±7 [a,c]	34±6
LVEDD [mm]	pre	59±8	63±9	63±9	62±8
	mid	57±9 [b]	58±8 [d]	59±8 [d]	61±8
	post	55±8 [a,c]	57±7 [a]	56±6 [a,b]	60±5
NYHA	pre	2.6±0.5	2.6±0.5	2.5±0,5	2.5±0.6
	mid	1.9±0.6 [b]	1.7±0.6 [d]	1.7±0.5 [d]	1.9±0.2 [d]
	post	1.6±0.6 [a]	1.5±0.6 [a,c]	1.3±0.5 [a,c]	2.0±0.5 [a]
peak VO_2 [ml min^{-1} kg^{-1}]	pre	16±5	15±4	15±4	16±4
	mid	18±4 [b]	16±3 [d]	18±5 [d]	17±4
	post	20±4 [a]	18±4 [a,c]	22±5 [a,c]	17±3

[a] post vs pre: $p<0.01$
[b] mid vs pre: $p<0.05$
[c] post vs mid: $p<0.01$
[d] mid vs pre: $p<0.01$
[e] post vs mid: $p<0.05$

Multiple Regression

Pro-BNP

Before the intervention no correlation existed between pro-BNP and EF, LVEED, NYHA and pVO_2 ($r=0.26$, $p>0.05$). After the intervention a clear correlation showed between EF (part $r=-0.33$, $p=0.0039$) and pVO_2 (part $r=-0.25$, $p=0.035$); r mult regr $=0.44$, $p=0.0035$).

NYHA

The improvement in NYHA classification correlates with the increases in EF (part corr $r=-0.28$; $p< 0.017$), but not with the changes in NT-pro-BNP, LVEED or pVO_2.

Ejection Fraction (EF)

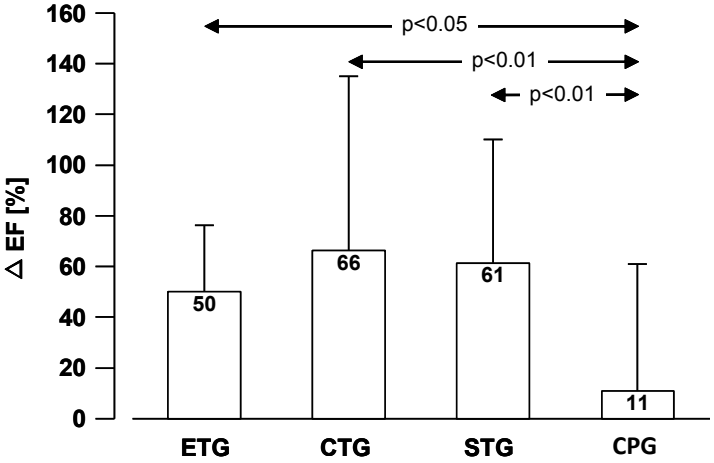

Figure 15: Changes in the EF expressed in Percentage.

LVEDD

Figure 17 shows the changes in LVEDD in the three intervention groups and the comparison group (CPG). LVEDD improved in all groups slightly, but only the STG demonstrated a significantly higher reduction in diameter (-11%; p<0.05) compared to the CPG.

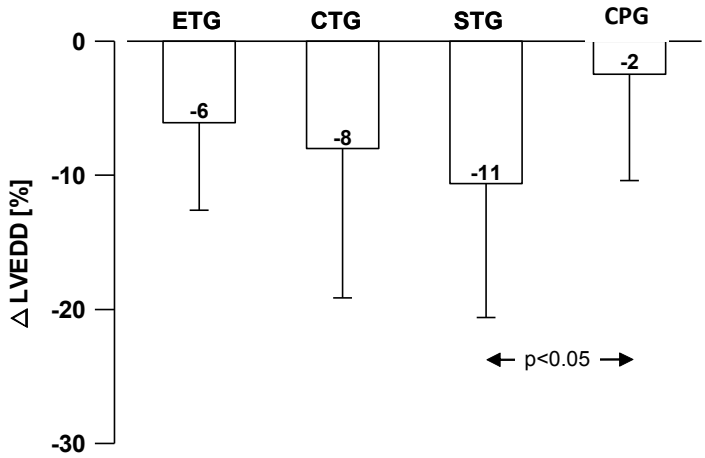

Figure 16: Changes in the LVEDD expressed in Percentage.

NYHA Classification

All exercise groups showed a significant improvement of NYHA classification and were reclassified by one class. Expressed in percentage this equated to -39% and -47% compared to the CPG with -16% of the baseline measurement, whereby the CTG and the STG showed again the greatest increase with -42% and -47% ($p<0.01$) respectively.

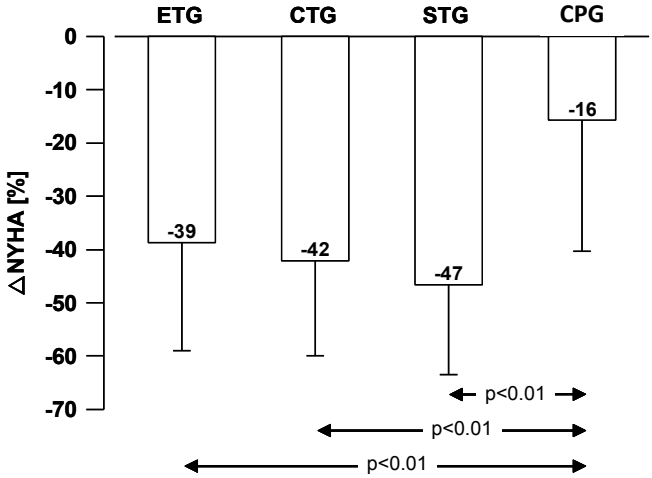

Figure 17: Changes in the NYHA Classification expressed in Percentage.

Peak VO_2

The peak VO_2 showed no significant changes in the CPG, but again significant changes in all training groups. Especially the STG showed the greatest increase from 15 to 22 ml min^{-1} kg^{-1}. In percentage the mean increase ranged between 24% and 53% compared to the CPG with 5% of the baseline measurement (Fig. 19), whereby the STG showed the greatest increase with 53% ($p<0.01$).

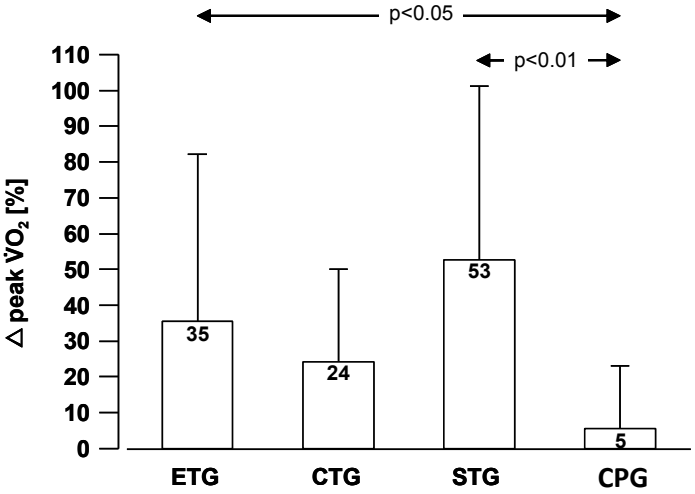

Figure 18: Changes in Peak VO_2 expressed in Percentage.

Heart Rate and Haemodynamics in the Cycle Ergometry

Table 14 shows the data of the pre, interim and post cycle ergometry testing regarding heart rate (HR) and blood pressure (RR). Significant changes were only found in HR behaviour of the STG and in systolic blood pressure of the CTG.

Table 14: Heart rate and blood pressure behaviour in the cycle ergometry.

		ETG	CTG	STG	CPG
HR [min^{-1}]	pre	74±13	77±16	77±8	70±16
	int	72±13	77±15	75±9	69±14
	post	71±12	77±16	74±10 [f]	67±8
RR sys [mmHg]	pre	121±16	129±13	122±15	140±19
	int	126±18	126±14	116±18	132±13
	post	123±21	119±13 [d,e]	118±14	129±29
RR dias [mmHg]	pre	76±8	81±8	78±5	83±10
	int	80±10	80±4	78±7	80±10
	post	78±5	79±5	77±7	76±13

[a] post vs pre: p<0.01
[b] int vs pre: p<0.05
[c] post vs int: p<0.01
[d] int vs pre: p<0.01
[e] post vs int: p<0.05
[f] post vs pre: p<0.05

Maximal Heart Rate and Maximal Workload in the Cycle Ergometry

Table 15 presents the maximal heart rate and maximal workload data of the cycle ergometry. The ETG showed a significant increase of the maximal performance comparing the pre vs. the interim and the post vs. pre testing ($p<0.01$) as well as post vs. interim ($p<0.05$). The STG also had a significant increase from interim to post testing ($p<0.05$). The maximal HR changed significantly in the CTG and CPG.

Table 15: Maximal heart rate and work load in the cycle ergometry test.

		ETG	CTG	STG	CPG
W_{max} [watts]	pre	98±23	84±28	89±34	100±16
	int	117±30 [d]	85±23	98±36 [b]	98±13
	post	109±29 [a,e]	86±30	95±36	98±21
HR_{max} [min^{-1}]	pre	122±26	127±26	125±26	124±19
	int	122±26	133±28	124±28	113±17 [b]
	post	118±27	117±27 [e]	123±26	106±15 [a]

[a] post vs pre: $p<0.01$
[b] int vs pre: $p<0.05$
[c] post vs int: $p<0.01$
[d] int vs pre: $p<0.01$
[e] post vs int: $p<0.05$
[f] post vs pre: $p<0.05$

Blood Lactate Behaviour in the Cyle Ergometry

Figure 20 shows the blood lactate behaviour in the cycle ergometry in all four groups (intervention and comparison). There were no significant changes in lactate values at all test points. However, the CTG shows a tendency to a right shift, which possibly means a lower energy demand at the same work rate.

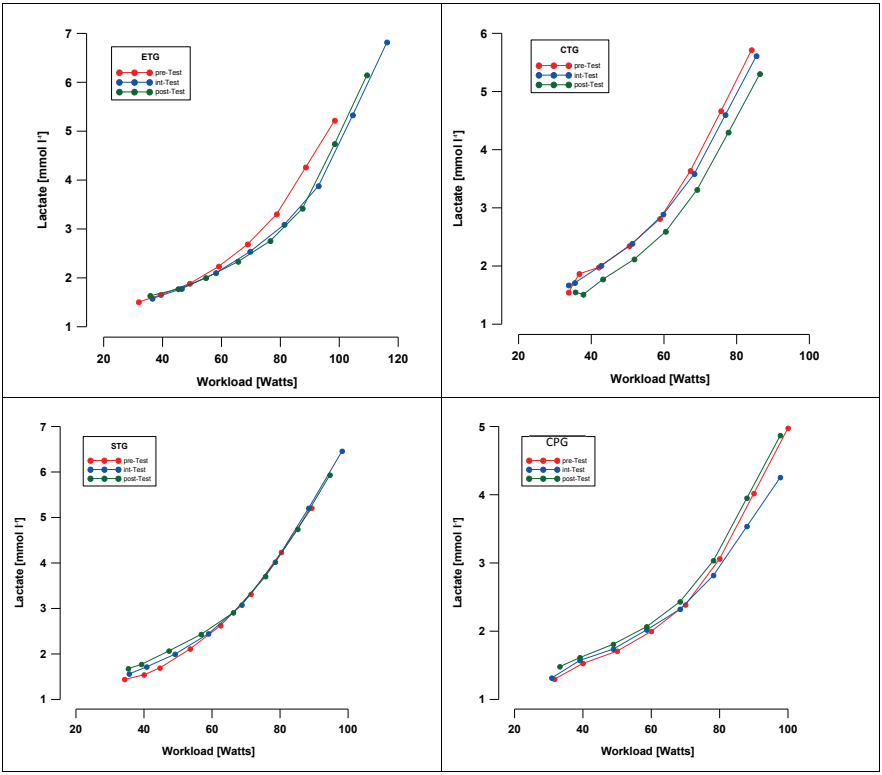

Figure 19: Lactate behaviour in all cycle ergometry tests of all intervention groups and the comparison group (CPG).

Heart Rate Behaviour in Cycle Ergometry

Figure 21 shows the changes in heart rate behaviour during the cycle ergometry of the three intervention groups and the comparison group. The only significant improvements regarding HR were demonstrated in the strength training group. Also see table 14.

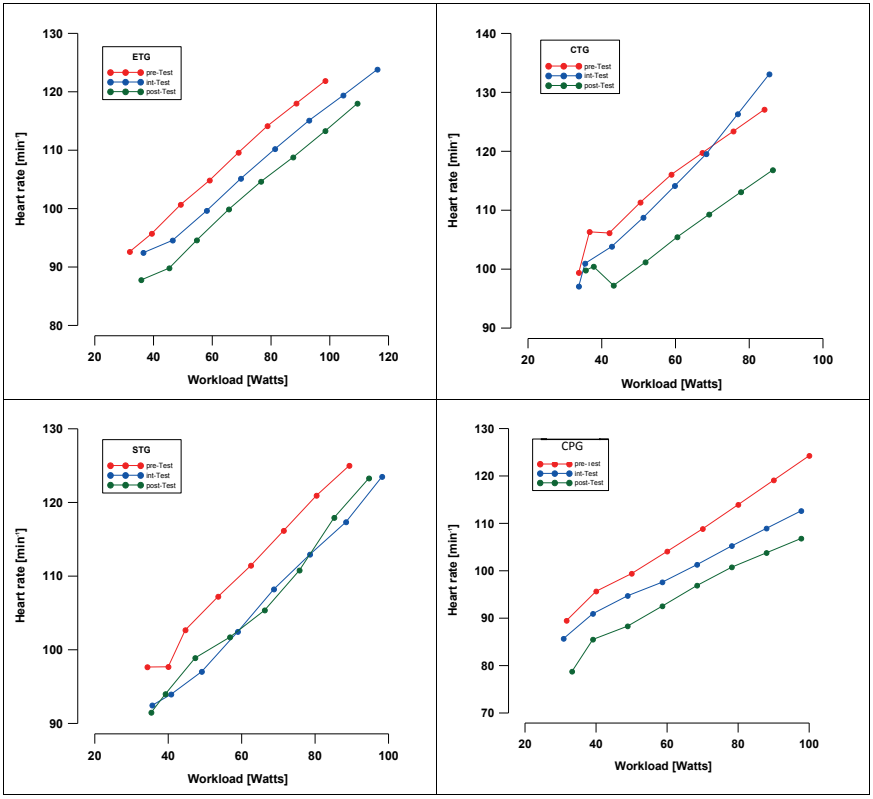

Figure 20: Heart rate behaviour in all cycle ergometry tests of all intervention groups and the comparison group (CPG). For details refer to tables 14 and 15.

Blood Pressure Behaviour in the Cycle Ergometry

Figure 22 presents the blood pressure (RR) changes of the pre, interim and post cycle ergometry testing. Significant changes were only found in the circuit training group regarding systolic blood pressure. Also see table 14.

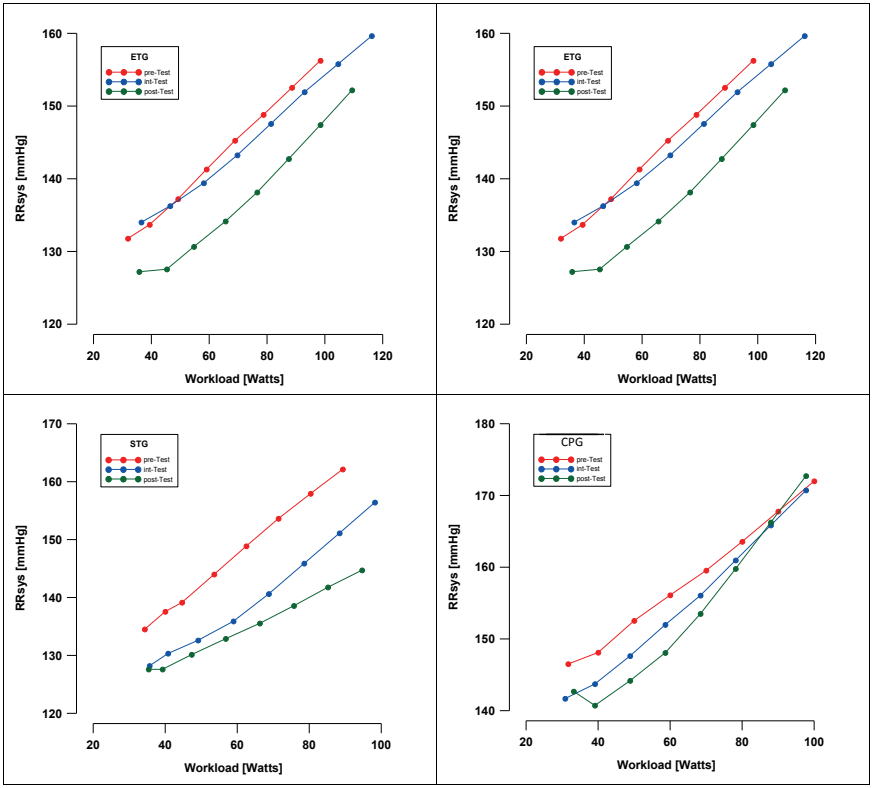

Figure 21: Blood pressure behaviour in all cycle ergometry tests of all intervention groups and the comparison group (CPG). For details refer to table 14.

Heart Rate * Systolic Blood Pressure in the cycle ergometry

The *Rate-Pressure-Product* (RPP) is presented in figure 23 and shows no significant effects in any of the four groups. However, a clear tendency of improvement can be observed in all three training groups – especially in the circuit and strength training groups.

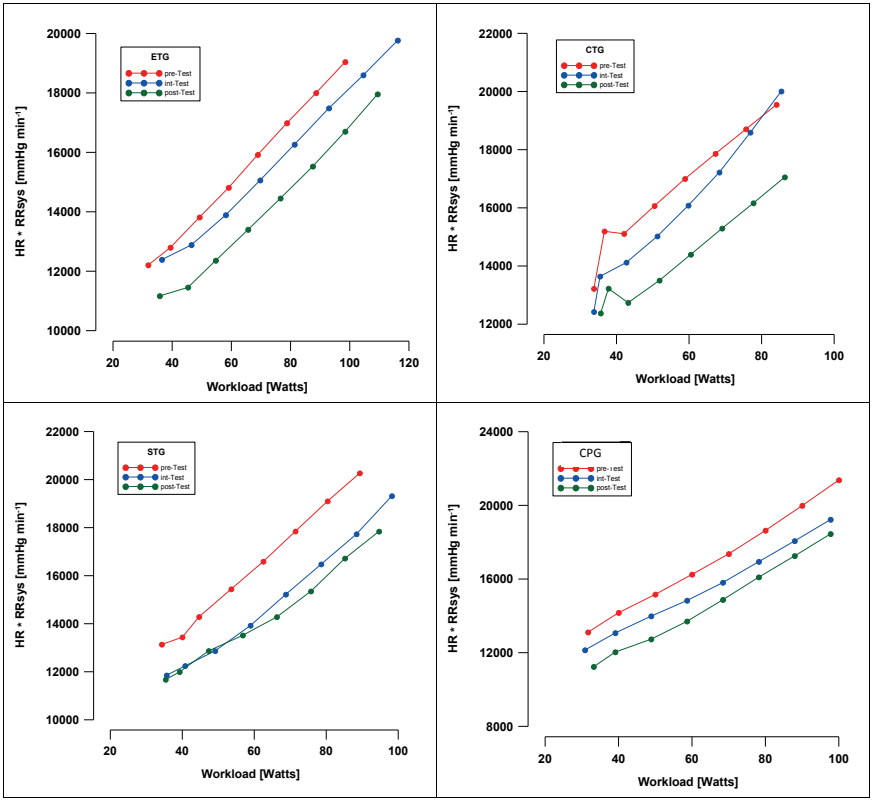

Figure 22: Heart rate * systolic blood pressure in all cycle ergometry tests of all intervention groups and the comparison group (CPG). For details refer to table 16.

Strength Performance

The results of the strength tests presented in table 16, show significant changes in the ETG regarding the leg press between pre vs. interim as well as post vs. pre testing. Similar results also apply to the bench press and the rowing seated test exercises. Even greater improvements were found in the CTG and STG, e.g. the leg press performance of the STG increased from 19 kg (190 N) to 34 kg (340 N). The CPG also showed minor changes compared to the intervention groups, which nevertheless were significant in the leg press and rowing seated test.

Table 16: Results of the 12-RM Strength Tests

		ETG	CTG	STG	CPG
Leg press [kg]	pre	21±8	23±7	19±9	26±10
	int	25±10 [d]	29±8 [d]	30±11 [d]	30±12
	post	27±11 [a]	33±12 [a,e]	34±13 [a,e]	32±12 [f]
Bench press [kg]	pre	22±8	24±7	22±9	30±13
	int	25±9 [d]	31±11 [d]	35±12 [d]	33±12
	post	26±9 [a,e]	37±12 [a,c]	39±15 [a,e]	34±12
Rowing seated [kg]	pre	28±10	29±8	25±12	32±14
	int	30±11 [d]	37±10 [d]	38±14 [d]	39±13
	post	33±11 [a,c]	43±11 [a,c]	42±15 [a,e]	42±15 [a]

[a] post vs pre: p<0.01
[b] int vs pre: p<0.05
[c] post vs int: p<0.01
[d] int vs pre: p<0.01
[e] post vs int: p<0.05
[f] post vs pre: p<0.05

Blood Pressure Behaviour during the Strength Training Intervention

In table 17 the exemplary blood pressure results during the exercise *Leg-press* are presented. Because of the amount of muscle mass involved in this exercise the greatest blood pressure increases can be expected here, compared to other exercises using smaller muscle groups. 6 patients were tested – 3 patients in the conventional strength training group with a mean work duration of 45s of leg-pressing and 3 patients in the circuit group performing a mean work duration of 60s.

Table 17: Exemplary blood pressure of the STG (n=3) and CTG (n=3) during the leg press exercise

		Strength TG					Circuit TG				
Parameter		Pat.1	Pat.2	Pat.3	$\bar{X}$	±	Pat.4	Pat.5	Pat.6	$\bar{X}$	±
Syst. BP	Min	97.3	114.0	124.0	111.8	13.5	167.0	100.7	154.7	140.8	35.3
	Max	130.7	119.7	158.0	136.1	19.7	186.0	116.3	190.0	164.1	41.4
	$\bar{X}$	116.9	116.9	143.8	125.9	15.6	177.9	109.7	173.1	153.6	38.0
Diast. BP	Min	58.0	42.3	71.0	57.1	14.4	98.0	70.3	76.7	81.7	14.5
	Max	74.3	48.3	88.0	70.2	20.2	108.0	79.0	100.0	95.7	15.0
		66.1	46.3	81.4	64.6	17.6	103.8	75.0	93.0	90.6	14.6
Med. Press.	$\bar{X}$	91.5	81.6	112.6	95.2	15.8	140.8	92.3	133.1	122.1	26.1
HR	$\bar{X}$	78.8	81.9	91.7	84.1	6.7	88.8	81.9	108.4	93.0	13.7
RRP	$\bar{X}$	9210.1	9572.5	13189.2	10589.3	104.8	15794.9	8986.1	18766.2	14287.1	523.1

Health Related Quality of Life (HRQL)

The HRQL measured by the Minnesota living with Heart Failure Questionnaire (MHFQ) showed no significant improvements in any of the groups. However, a tendency for improvement appeared in the endurance training group, the strength training group and the comparison group. The circuit training group, despite their greatest improvements in cardiac parameters showed no in health related quality of life at all.

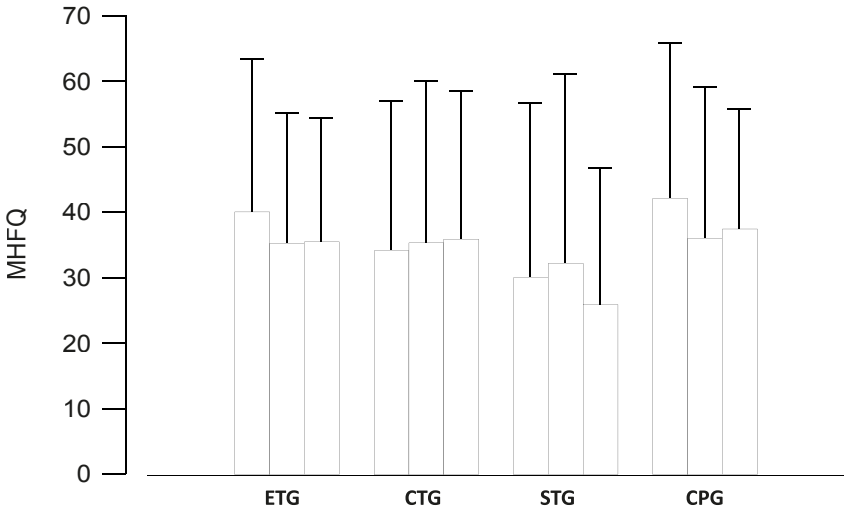

Figure 23: HRQL in all exercise groups and the comparison group (CPG).

Mortality Data

Table 18 shows the mortality rate of all the patients in the three training groups with 3.1% whereas the control group just had a 28% chance of mortality within 30 weeks. The mortality rate of the training groups is therefore significantly lower ($p<0.001$). The CPG showed a slightly higher mortality rate than the exercising groups, but still significantly lower than the control group.

This data was collected additionally to the aforementioned other measurements and therefore include the control group (n=25). The total number of patients for this parameter was n= 105.

Table 18: Mortality rates in the different groups.

	Mortality
Control Group	28%
CPG (non-training)	5.6%
Training Group	3.1%

The changes in mortality are presented in figure 25 and show a significantly better outcome in the exercise groups and the dietary comparison group compared to the control group. Also see table 18 for details.

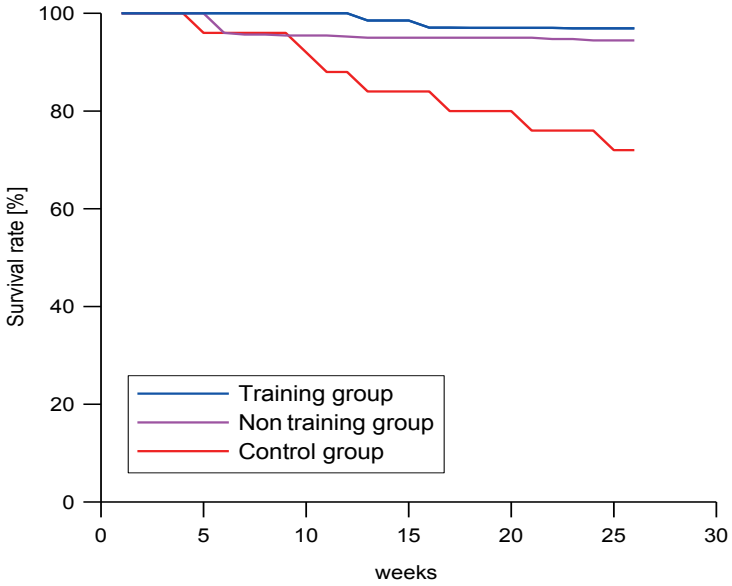

Figure 24: Survival rate of all training groups vs. the control group (left) and all the training groups vs. the non-training comparison group (CPG) and the control group (right)

Hospitalisation Data

There was a significant change in the hospitalisation rate between the training groups and CPG ($p<0.01$) within 30 weeks which is presented in table 19. The hospitalisation rate of CPG was 33% for that duration compared to 15% in the exercise intervention groups and even higher in the control group with 36% over the same period of time. This data refers to a total n= 96 (including 78 intervention and comparison group patients and 18 control group patients).

Table 19: Hospitalisation rates in the different groups

	Hospitalisation
Control Group	36%
CPG (non-training)	33.3%
Training Group	15.4%

Figure 26 visually presents the hospitalisation rate in all groups during 30 weeks. For details refer to table 19.

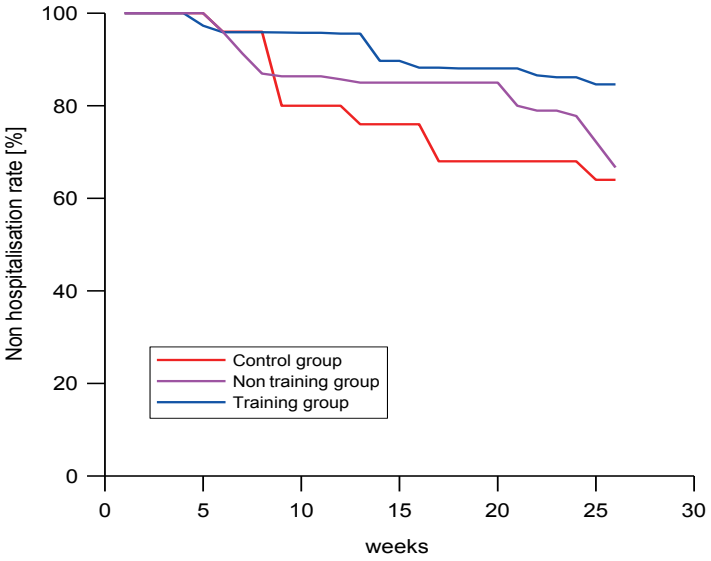

Figure 25: Hospitalisation rate of all the training groups vs. the control group and all the training groups vs. the non-training comparison group (CPG) and the control group.

3.4 Discussion

Exercises that use higher intensities and/or training methods that are typically applied in a sportive environment have long been considered as an absolute contra-indication for CHF patients. Due to adequate therapy using similar methods there is evidence that a systematic training can improve many pathophysiological mechanisms of CHF. However, the question is, what type of exercise and at what intensity produces these effects, which include anabolic adaptations and anti-inflammatory processes in the skeletal musculature [190,191]? The endothelium dysfunction can also be positively influenced by physical training similar to the coronary vessels [192,193] as well as positive effects on neurohormonal dysfunction due to the reduction of catecholamine levels, e.g. angiotensin II, aldesterone and vasopressin [194].

Over the whole duration of the six months intervention, using all described exercise interventions not one health relevant incident occurred during the training. Hence, the initial hypothesis that "strength training interventions are safe to be used in CHF patients applying high intensities and longer durations" has to be accepted.

One way to demonstrate these positive training adaptations regarding the performance and exercise tolerance of CHF patients are changes in the VO_{2max} or VO_{2peak}, which has been shown to increase as a mean value between 11.5% and 29% [182,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210]. This was also the case in this study. All exercise groups showed a significant increase between 24% and 53% compared to the CPG with 5% of the baseline measurement, whereby the STG showed the greatest increase with 53% ($p<0.01$), which was unexpected. The reason for this finding might be that at a given workload less stress is put on the energy metabolism if the maximal strength of the leg muscles is increased. Therefore, the hypothesis that "the endurance performance can be improved by applying different exercise modalities" has to be accepted. These results are similar to the findings of GIALLAURIA et al. (2008) [211] with an increase of Peak VO_2 by 31%, the same improvements as in the study of CALLAERTS-VEGH et al. (1998) [212] and also DEMOPOULOS et al. (1997) [213] (+30%).

Other publications have demonstrated that the maximal workload in the cycle ergometery can increase through exercise interventions in heart failure patients by an average of 15 to 32 Watts as well as the exercise duration of 12-45% and longer walking distances of 16% to 65% [182,189,195,199,204,205,207,208,209,210,214,215]. But all

of the above studies used primarily an endurance exercise as an intervention, which were predominantly carried out using a cycle ergometer. Whereas, only very few studies used strength training interventions. The latter showed changes in maximal strength by a mean increase of 28% [189,204,205], but also a positive change of VO_{2max} and the overall performance in the cycle ergometry [204]. This also applies to this study as presented above, which can be explained when considering the catabolic situation OF any chronic internal disease and especially of CHF patients. Recent data are especially interesting regarding the immunological changes and the catabolic situation of the skeletal musculature in CHF patients. These changes are concerning a significant decrease of the NT-pro-BNP caused by a combined strength and endurance training in NYHA III-IV patients (from 2428pg ml^{-1} down to 1900pg ml^{-1}) [200,201]. The changes in NT-pro-BNP were not quite as great in this study. However, there were significant reductions in this parameter in the ETG, which could not be demonstrated in the STG or the CTG. This stands in contrast to other parameters such as EF and LVEDD. Whether this is a coincidence or is a general characteristic of endurance training and/or strength training interventions needs to be investigated by future research.

It is worthwhile mentioning that in the context of NYHA-classification, endurance as well as strength training methods can produce an improvement by an average of 0.86 classes [205,206,208,211]. Thus, all the patients in this study improved by a whole class. These significant improvements ranged from -39% and -47% respectively compared to the CPG with only -16% of the baseline measurement, whereby the CTG and the STG showed again the greatest increase with -42% and -47% ($p<0.01$). The above changes are especially remarkable as all patients received optimised medication schemes; according to the European Society for Cardiology before any other intervention was introduced. This scheme was not altered in any way throughout the duration of the study.

These results are coherent with the changes in the EF and prove the significance of catabolic changes caused by CHF including neurohormonal adaptations and the role of strength training in this context. Some studies showed an increase of the ejection fraction by 6.3% and an improvement of the stroke volume by 27% and at the same time a significant reduction of the LVEDD [197,201,206,208,214]. This is similar to the data of this study, which showed a rather unexpected dramatic change of the EF (50% to 66%) in all exercise groups compared to the CPG, which had an improvement of just 11%. Whereas the ETG showed an increase of 50% ($p<0.05$ vs. CPG), the CTG with 66% and the STG with 61% (both $p<0.01$ vs. CPG).

The initial hypothesis that "cardiac specific parameters can be improved by specific exercise interventions" therefore has to be accepted.

These changes might be caused by improving endothelial function, etc. A study conducted by KELLERMAN et al. (1990) [216] using a high intensity arm ergometry exercise (90% maximal performance) also showed a remarkable increase of the EF by 40% (increasing from 30.1% ±9.5 to 42 ±12.2 in 36 months). The same study demonstrated an increase of peak power from initially 43.5 ±15.2 Watt to 62.5 ±13.3 (+44%).

The findings of this study are also confirmed by a review by BRAITH and BECK (2008) [217]. This article presents evidence that improvement of skeletal muscle phenotype (muscle mass, fibre morphology, and histochemistry) should be a fundamental goal of rehabilitation in patients with CHF. Moreover, Resistance Training may be the preferred exercise modality when targeting the periphery for muscle phenotype adaptation [218].

The increases in strength performance were naturally higher in all the training groups and as expected the highest strength gains were achieved in the STG and CTG ($p<0.01$), but even the ETG showed significant changes. These are predominantly because of the high proportion of strength necessary for the leg work and partially to stabilise the upper body (arms etc.). One argument against resistance training in cardiac rehabilitation in the past always was the possibility of dangerously high blood pressure peaks. This could be proven wrong as the systolic maximum value during hypertrophic strength training only reached 151.1±mmHg and during circuit training 193.3±5.1 mmHg which probably was due to the significantly longer work duration of 60s compared to 45s and much shorter break between each set of only 30s against 2 min during conventional strength training. Not a single cardiac incidence occurred during the whole study in any of the training groups.

However, the most important results are the dramatic differences in the hospitalisation rate and also in the survival rate of the training group vs. the control group ($p<0.01$). The underlying physiological reasons for this are manifold and were explained previously. This has hardly been demonstrated by any previous study. The impact of this for any health system, insurance and government policy can hardly be overestimated.

The above described results underline the essential role of exercise training for CHF patients. However, there is still an on-going discussion about the specific type and/or method, the optimal intensity and exercise duration. This study tried to

contribute towards answering certain questions in this discussion, especially as using specific strength training methods is a relatively new approach in the therapy of CHF. This is of particular interest considering the muscular dysfunction and the disease specific muscle atrophy respectively [175,176].

CONCLUSION

The patients of all training groups could be reclassified according to the NYHA-system by one class. It can also be stated that at no time cardiac problems occurred. Furthermore, it should be pointed out that an outpatient training therapy finds a high acceptance in these patients and is practicable at the same time. The results and experiences point at the safe feasibility of different outpatient training interventions and suggest specific positive adaptations in patients with chronic heart failure which also lead to a lower hospitalisation rate. There are clear hints that the therapy spectrum could be supplemented significantly in the near future by specific training interventions. The financial implications for any health care system are also highly relevant and will be addressed in more detail in the final discussion.

4 COPD STUDY 1

Effects of a High Intensity Resistance Training on Respiratory Function and Functional Exercise Capacity in Patients with Chronic Obstructive Pulmonary Disease (COPD)

4.1 Objectives

An effective treatment of chronic obstructive pulmonary disease (COPD) requires different therapy approaches. Yet, giving up smoking must be considered the most important intervention, because this can affect the process of the disease the most [219]. Additionally, the patients require a pharmacological therapy. Systematic physical training is another treatment form, which not only contributes to a general stabilisation of the patient's constitution, but is also considered to improve the HRQL. The health and physical decline of COPD patients is also caused by the aforementioned *vicious circle*, consisting of illness - caused by inactivity and the progressive worsening of the disease symptoms. The goal of every exercise therapy should be to end this vicious circle. In principle, numerous types of exercise show a positive effect on the course of the disease.

However, the effectiveness and efficiency of the individual measures can vary significantly, especially when considering the patient's compliance to exercise when significant dyspnoea is experienced, i.e. during endurance training. This can also be described as the toleration of the exercise interventions which behave likewise. Thus, different investigations have already proven the positive influence endurance training has on the health situation of COPD patients [219,220]. Resistance exercises have also shown significant effects [221,222], but these are usually performed at relatively moderate intensities. Contrary to these studies, this research project examined the effects of a 12-week outpatient pulmonary rehabilitation programme on exercise capacity and pulmonary function in COPD patients, applying a high intensity hypertrophic strength training. The decision for this form of treatment was based on the observation that COPD patients are limited in their physical activity by their decreased muscle strength, rather than an insufficient functioning of the cardio vascular system.

Additionally, it is likely that an increased production of the hormone testosterone initiated by this kind of strength training might have a positive effect on symptoms and quality of life for these patients who suffer regularly from a

disease-specific testosterone deficit [223,224,225]. Taking this into consideration, intensive endurance training can even cause an acute reduction in testosterone plasma concentration [226]. Above this, a pilot study showed that the patients tolerated high intensity strength training better than endurance training. This is probably because of its intermittent structure (short intensive bouts followed by relatively long breaks).

We therefore hypothesised that high intensity hypertrophic strength training has a positive effect on respiratory function, endurance, strength and health-related quality of life in patients with COPD.

4.2 Methods

4.2.1 Subjects

The cohort of this study originally consisted of 40 COPD patients (GOLD II to IV) who were stratified and allocated to an intervention group (n= 25) and a control group (n= 15). The different group size was based on the assumption that a higher number of patients would drop out of the intervention group due to the novel approach of using a high intensity strength training. This assumption was proved wrong due to an increased compliance in the intervention group.

Thus, the results presented refer to 28 COPD patients GOLD stages II to IV. The intervention group consisted of 21 patients who completed the study and the control group, which finished up with 7 patients. Details of the cohort are presented in table 20.

Table 20: Specifications of the patients who completed the study in the intervention and control group (n=28).

Age (years)	55.7 $\pm$ 6.9
Weight (kg)	70.6 $\pm$ 13.3
COPD Stage	2.6 $\pm$0.9
FEV_1	55.9 $\pm$12.8
Male; n=12 (%)	43
Female; n=16 (%)	57

Declaration of Consent:
All subjects had to sign a declaration of consent before being considered for one of the study groups. The patients received information in writing about the overall study design, the specific intervention and benefits and risks associated with it. Furthermore, a personal interview was held by a physician.

Study Termination:
Every patient could terminate the study at any time.

Inclusion Criteria:
Patients could participate in the study if they fulfilled the following criteria:

- Anamnesis of COPD, characterised by cough and sputum production for more than 2 years, irreversible changes in FEV_1, and exercise induced dyspnoea
- FEV_1: 35–70%
- No clinically significant comorbidity (according to the opinion of the treating physician)
- Age: 40 to 70 years
- A minimum performance in the cycle ergometry of 40 W for 3 min

Exclusion Criteria:

- Unstable and/or life threatening underlying condition other than COPD
- Severe acute infectious disease
- Cystic fibroses, active tuberculosis
- Malign lung tumour
- Medication or alcohol drug addiction
- Patients who are being treated for epilepsy
- Patients who have been involved in regular physical training in the past 6 months
- Co-morbidities: unstable insulin dependent diabetes mellitus, heart failure NYHA III or IV, acute orthopaedic problems

Intervention Group
The intervention group (STG) consisted of 21 subjects (10 male, 11 female) with an average age of 56.5 years (±6.9), a body weight of 73.2Kg (±21.9), and a FEV_1 performance of 54.9% (±13.8). The strongly differing FEV_1 values and an age difference of up to 20 years led to a heterogeneous performance. The 4 dropouts in this group were caused by a lack of interest in two cases and an acute exacerbation in the other two.

Control Group

The control group (CG) consisted of 7 subjects (2 male, 5 female) with an average age of 59 years (±8.9), a body weight of 68.1 kg (±8.6), and a FEV_1 mean value of 59.0% (±9.1). The smaller number of patients in this group was caused by dropouts, who did not participate in the re-tests. The reason for the high number of dropouts were: no interest 1, exacerbations 3, too much time spent on additional testing 4.

4.2.2 Experimental Procedures

Study Design

TEST PROCEDURES

Before and after the 12-week training intervention, both groups completed extensive baseline and retesting, each lasting 2 weeks. In two intermediate tests (each after 4 weeks), the respiratory function was measured additionally and the health-related quality of life – see figure 27. All subjects conducted daily peak flow measurements (in the morning and evening) and documented the results. Apart from these daily measurements, the control group (CG) members participated in all other tests, but were asked not to change their lifestyle at all.

The test profile was applied at baseline and after 12 weeks of intervention consisting of the following test: respiratory function test (BODY), cycle ergometry, strength test (12 RM) in 6 different exercises (see figure 27), flexibility test, health related quality of life questionnaire as well as testosterone measurements. In the two interim tests each after 4 weeks of intervention the respiratory function, the HRQL and testosterone levels were tested again. Furthermore, daily peak flow measurements were conducted by all patients in the morning and evening. Additionally, the depression profile of the patients was evaluated at baseline.

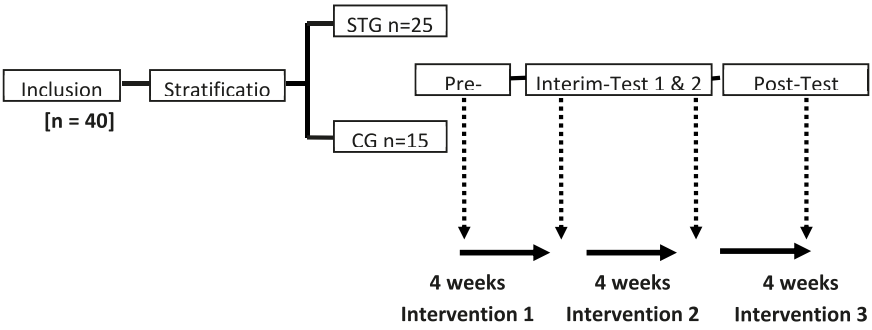

Figure 26: Schematic Study Design

INTERVENTIONS

The subjects of the intervention group (STG) underwent an outpatient exercise programme over 12 weeks using a high intensity hypertrophic strength training method, which was divided into three phases: (1) anatomical adaptation training (2 weeks), (2) high intensity hypertrophic training I (5 weeks), and (3) a high intensity hypertrophic training II with intensified eccentric work (5 weeks) – see table 21.

Table 21: 12-week progressive exercise regime of the intervention group

Training Phase	Contents
Anatomical adaptation	12 reps. / at the beginning 2, then 3 sets / pause:* 1 min. / submaximal intensity *a strength exercise specific stretching was accomplished during the pause **Exercises:** 6 exercises using machines were accomplished which trained large muscle groups respectively kinetic chains. Exercises for strengthening the abdominal muscles were carried out individually afterwards.
Hypertrophic phase 1	10 reps. / at the beginning 2, then up to 4 sets / pause:* 2 min. /maximal intensity **Exercises:** see above
Hypertrophic phase 2	8-10 reps. / at the beginning 2, then up to 4 sets / pause:* 2 min. / maximal intensity emphasizing the eccentric phase by using a "heavy negative" mode **Exercises:** 7 exercises using machines

During the muscle habituation phase, the intervention took place twice a week, in the next phase, three times per week. The training duration lasted 60 min at the beginning and 120 min in the last phase. A subject could miss as many as 4 (of 34) exercise sessions before his or her data were dismissed for statistical analysis.

In principle, large muscle groups were trained and/or complex exercises were accomplished using kinetic chains, as follows: (1.) leg press, (2.) leg curl, (3) bench press, (4.) lat pull, (5.) seated rowing, (6.) back extension, (7.) lateral trainer, and (8.) abdominal exercise (individually). Great attention was paid to a slow and technically correct movement execution and to the appropriate breathing technique – avoiding any *Vasalva* manoeuvre. The electro-mechanical training machines (Life Fitness, Munich, Germany) were used in order to ensure maximal training intensities.

The images below illustrate the order in which the exercises were conducted:

Figure 27: Impressions of the high intensity strength training
The illustrated patient initially was on oxygen substitution – after 6 weeks of intervention she did not any need oxygen therapy during the intervention and was able to reduce her overall oxygen consumption in a month by approx. 50%.

EQUIPMENT

Spirography/ Bodyplethysmograph (BODY)

The respiratory function measurements were conducted in all tests using the Master Screen equipment (Jaeger/Toennies, Hoechberg, Germany), at the same daytime under standardised conditions. Among other parameters, the forced expiratory ventilation in 1s and the flow resistance were measured.

Peak Flow
The daily peak flow measurement was solely carried out by the patients, both in the morning and evening, using a peak flow meter (Aventis Pharma, Bad Soden, Germany).

Health Related Quality of Life (HRQL) Questionnaire
For the determination of the health-related quality of life, the St. George's Respiratory Questionnaire (SGRQ) was used. Each question was read out to the individual patient, and the answer was marked by the interviewer.

Depression Symptoms Questionnaire
The BDI questionnaire was used for identifying any underlying depression symptoms in COPD patients and enabling the investigators to identify gender differences of disease specific effects on mental health.

Cycle Ergometry

The cycle ergometer tests were conducted using the Life Cycle 9500 of the company Life Fitness (Munich, Germany). The graded ergometry started at 40 W and was increased by 10 W per stage, each with a duration of 2 min.

Strength Training Devices

The strength training equipment of the company Life Fitness (Munich, Germany) uses electro-mechanic technology, which enables the user to build up a resistance in 1kg steps. The resistance shown in kg on the display equals the force produced in N (times 9.81), which made it possible to use the equipment for training as well as diagnostic devices.

4.2.3 Statistics

The data is expressed as mean $\pm$ SD. Non-parametric test procedures were applied, because of the small sample size and the attested variance homogeneity by the F-Test. Hence, the data for unpaired samples was analysed using the *Mann-Whitney U-Test*. The values of the initial tests, intermediate tests, and retests were compared between groups using the *Wilcoxon* test for connected samples. P-values <0.05 were considered significant. The data was analysed according to the *Per-Protocol* procedure.

4.3 Results

Respiratory Function: *FEV$_1$*

The FEV_1 shows a significant increase in the treatment group from 56.8% ±17.1 to 62.1% ±19.1; difference: 5.3% – see figure 29, whereas in the control group, only a non-significant change was found from 60.5% ±15.9 to 64.0% ±16.3; difference: 3.5% – see figure 30. The air flow resistance showed no significant changes.

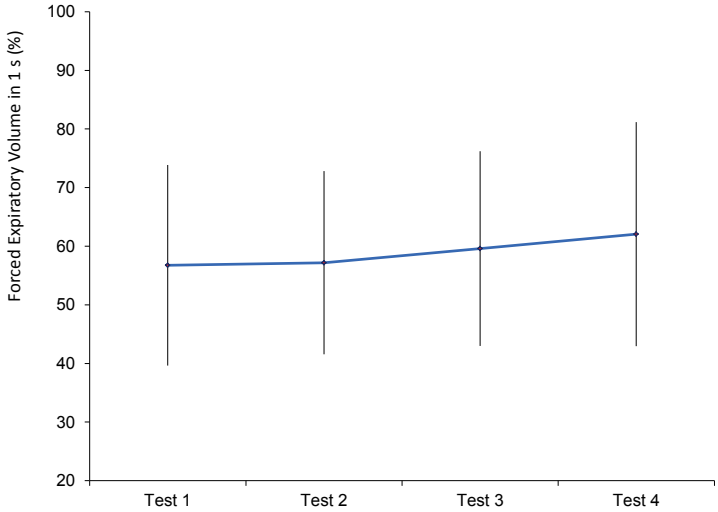

Figure 28: The mean FEV_1 performance and SD of the intervention group

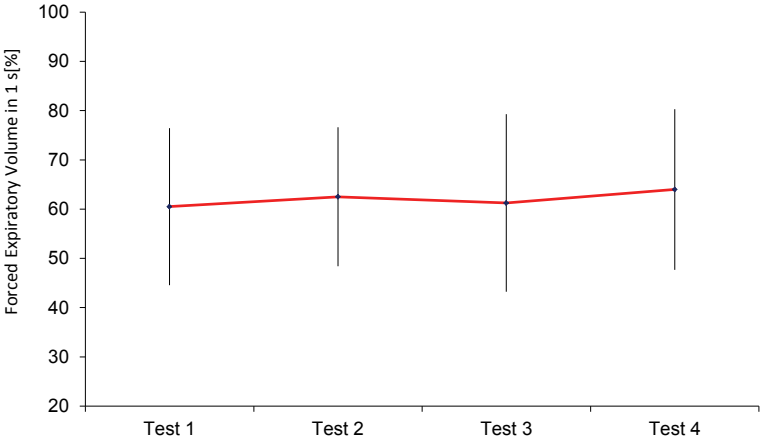

Figure 29: The mean FEV_1 performance and SD of the control group

Respiratory Function: *Peak Flow*

The peak flow data only demonstrated a non-significant increase in the intervention group, both in the morning (15L/min) and in the evening (20L/min) - see figures 31 and 32. In contrast, the trend line of the control group shows a much smaller increase in the morning and remains nearly unchanged in the evenings for the duration of the investigation.

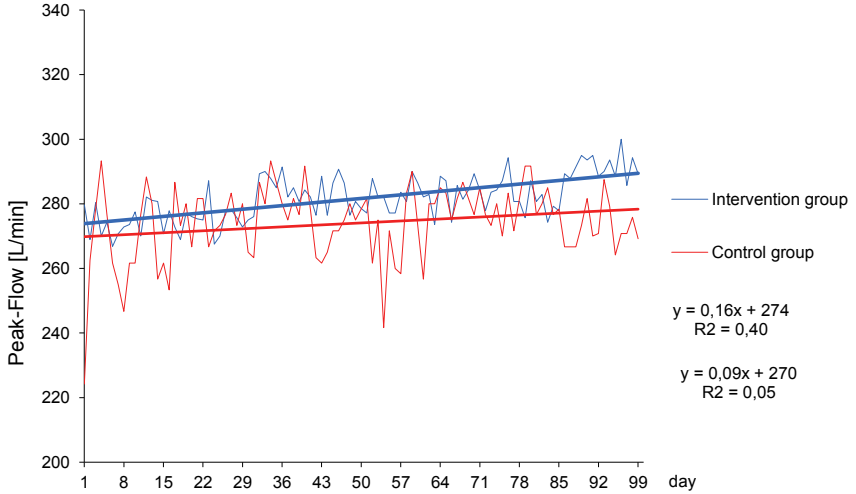

Figure 30: The average peak-flow performance of intervention (STG) and control group (CG) in the morning.

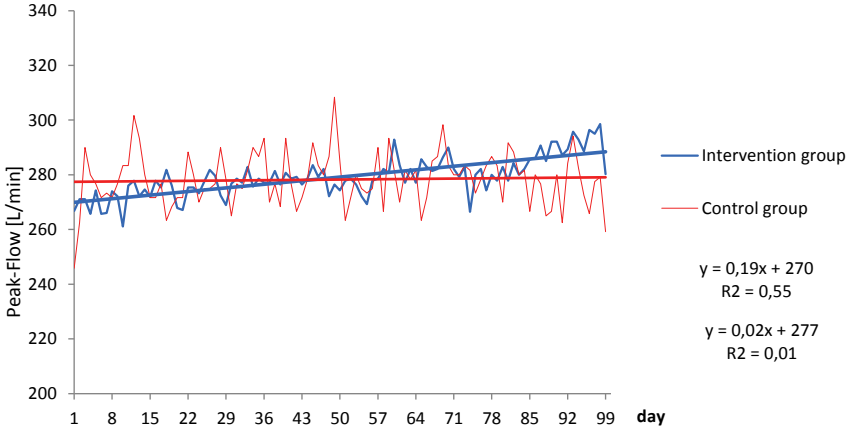

Figure 31: The average peak-flow performance of the treatment (STG) and control group (CG) in the evening

Cycle Ergometry

The maximum performance of the intervention group (see Figure 33) in the incremental ergometry increased significantly (p< 0.01) by 21.9W (18.7%). In contrast, the performance of the control group increased by a non-significant 2.9W (4%).

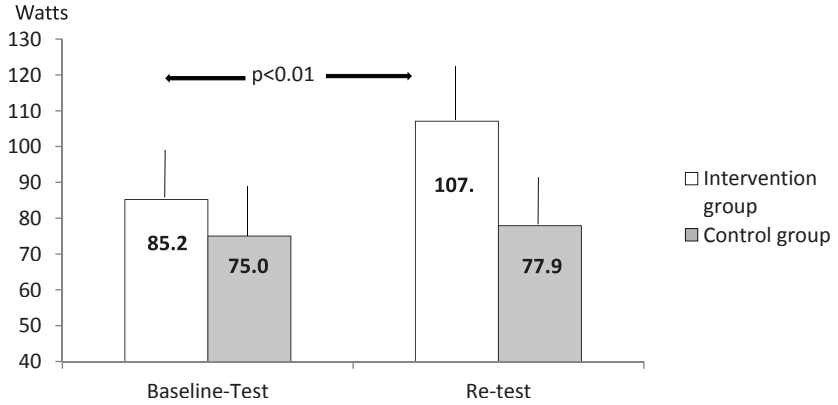

Figure 32: Maximal cycle ergometry workload (W) of the intervention (STG) and control group (CG) in the baseline and retest.

Performance at 4 mmol/L blood lactate

The performance in Watts (W) at the 4 mmol/L threshold is presented in figure 34. The intervention group showed a significant increase in performance by 9.1W (p<0.01;**) whereas the control group presented no significant changes.

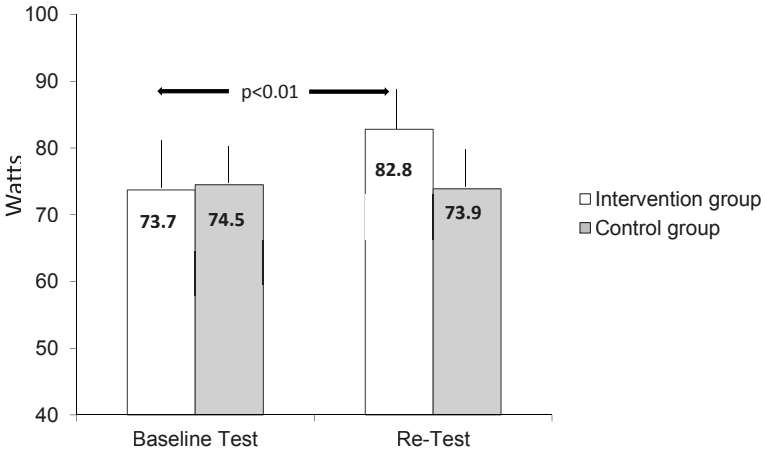

Figure 33: Cycle performance at 4mmol/L blood lactate

Strength Performance

The increases in strength performance in the 12 RM-Test were improved significantly in all test exercises in the intervention group ($p<0.01$;**) and also showed the same significant differences compared to the control group – except for the back extension exercise where only a significant difference of $p< 0.05$ was achieved. The average increase in strength in all six test-exercises accumulated, was 36.8% within the 12 week training period – see figure 35.

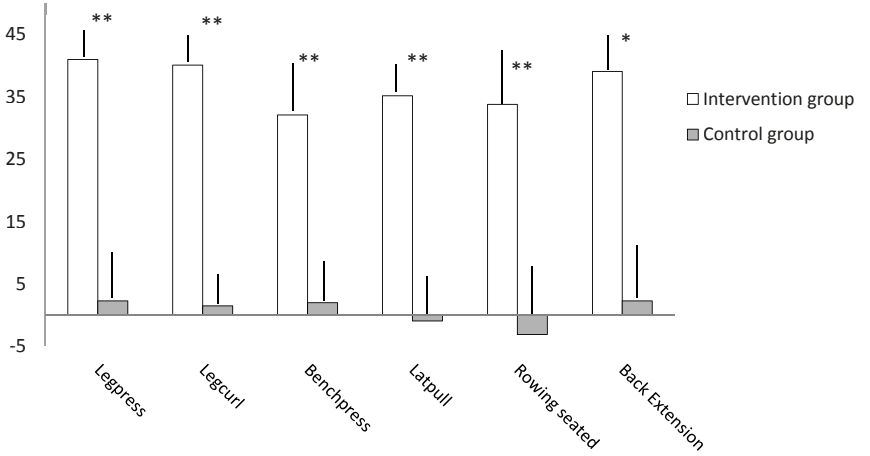

Figure 34: Comparison of the % changes in strength in the intervention and the control group.

Flexibility

The improvements in flexibility in the intervention group were all significant (* or **). The average increase in this group was 42.6%, whereas the control group showed no significant changes. The greatest improvements could be demonstrated in the quadriceps femoris with a mean value of 62.4%. The m. pectoralis major showed a clear imbalance between left and right of 13.7%. However, this difference was not significant.

Blood Testosterone

Figure 36 shows the changes in blood testosterone in both groups between baseline test and retest. Although there were 21 patients in the intervention group, only 15 samples were analysed due to faulty blood samples. The samples of the control group were complete. All subjects presented the typical testosterone deficit in COPD patients which was the primary objective for this measurement, as the frequency of blood sample taking would need to be at least daily, to reflect any chronic biological changes of this parameter in a valid manner. Hence, the increases of the intervention group of 0.6µg/L (7.8%) in free

testosterone and 0.6µg/L (35.3 %) of total testosterone are not suitable for deriving any conclusions.

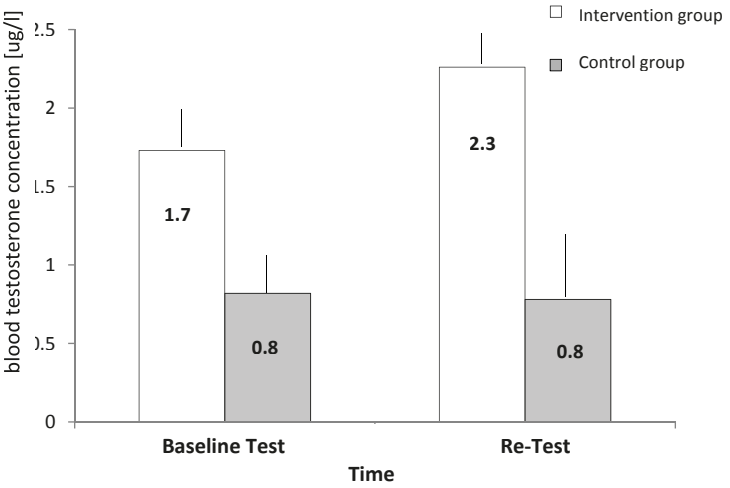

Figure 35: Comparison of total testosterone in the intervention group (n=15) and control group (n=7) from baseline to re-test.

Health-related Quality of Life (HRQL)

When comparing the data of the intervention group between the baseline test and the retest, a significant ($p < 0.05$) improvement could be demonstrated after an initial decline (see Figure 37). In the control group, a slight decline of the HRQL was observed. However, this decline was not significant.

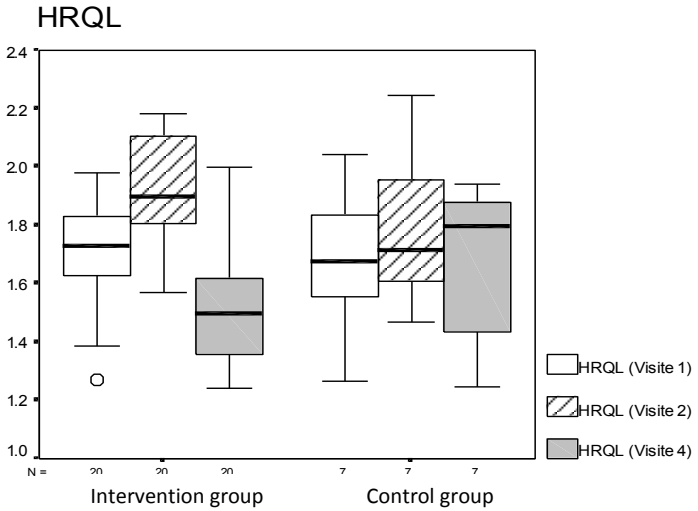

Figure 36: Changes in health-related quality of life for the treatment and control groups.
A decrease in the number of scored points means an increase in the HRQL and vice versa. The St. George's Respiratory Questionnaire was evaluated before the intervention (test 1), after 4 weeks (test 2), and after 12 weeks (test 4).

Depression Symptoms

All patients were initially tested for symptoms of depression using the BDI. This was relevant as any long-term disease will eventually provoke depressive symptoms. Within the overall cohort of 28 patients, 5 scored 18 points or above which shows a tendency for depressive symptoms and is therefore considered to be clinically relevant as presented in table 22.

Table 22: Individual BDI test sum scores of the cohort (n=28) at baseline. According to HAUTZINGER (1994), a value ≥18 should be considered as clinically relevant [227] (highlighted in grey).

∑-Value	N	%
3	1	3.6
4	3	10.7
5	2	7.1
6	1	3.6
7	4	14.3
8	2	7.1
9	2	7.1
10	3	10.7
12	2	7.1
14	1	3.6
16	1	3.6
18	1	3.6
19	1	3.6
20	1	3.6
26	1	3.6
34	1	3.6
Total	**28**	**100.0**

In table 23 the cohort is sub-divided into genders. This seems necessary as women and men are known to have gender-specific responses and/or coping strategies when chronically ill. In this cohort women scored with 14.50 points, more than twice as high as their male counterparts (7.00 points) and therefore significant ($p< 0.001$).

Table 23: Gender specific mean values of depression score sums.

Gender	$\bar{x}$	SD
Female	14.50	8.5
Male	7.00	2.1

Table 24 presents the relationship between scored BDI values and the duration of COPD and the disease history respectively. Those patients with a relatively short history of COPD (<18 months) scored the highest, although their mean value of

15.3 is clinically not relevant. There appears to be a tendency of lower depression scoring the longer the disease history. However, none of the effects are statistically relevant.

Table 24: Mean values of depression score sums relating to disease history/duration.

Group	COPD history	N	%	$\bar{x}$	SD
1	Since < 18 months	3	10.7	15.3	9.5
2	18 to < 120 months	9	32.1	11.6	7.1
3	120 to < 540 months	16	57.2	10.4	7.6

4.4 Discussion

The peak-flow data of the intervention group (STG) only shows a non-significant increase of 15 L/min and 20 L/min respectively. This was not found in the control group (CG). The FEV_1 performance of the intervention group increased significantly by 5.3% which confirms the tendency of the peak flow values. In this context, it would be interesting to observe the long-term effects of such an intervention on respiratory function. An explanation for this must remain speculative. This type of resistance training potentially compensates the degeneration of the active and passive movement apparatus that is caused by disease-specific deconditioning processes in a manner that cannot be achieved by endurance training. It is possible that the associated compensation of muscular imbalances, which cause a restriction of the thorax, is responsible for this effect. Beyond that, another effect is the strengthening of the auxiliary respiratory muscle. Both aspects could promote an increase in respiratory function [222]. Likewise, the potential reduction of swelling in the bronchial mucous membrane could be caused by anti-inflammatory processes that might be initiated by hormonal changes and this could have contributed to this positive effect. Another possible explanation is simply the increased strength which aids in the exhalation process – especially the m. pectoralis major. Also the breathing technique used during resistance training might have had similar effects to proper breathing exercises. So far, similar results have only been produced by endurance training in asthmatic patients [221], but not in COPD patients.

The ergometry data shows a significant improvement of the intervention group (21.9W = 18.7%) in comparison to the control group (2.9W = 4%), which partly results from improved movement coordination (warm up and cool down on the stationary cycle) [228]. However, such improvements cannot be explained purely by an improved coordination, since it is a quite simple technique. The better endurance performance was more likely caused by the increase in muscle mass, muscle power, as well as greater glycolytic capacity and changes in the enzymatic activity. This observation corresponds with the findings in healthy elderly subjects who showed that intensive resistance training has a positive effect on the oxidative metabolic capacity [218], which is contrary to adaptations in younger people in the same intervention. In this context, MALTAIS et al. demonstrated that COPD patients have a smaller amount of oxidative enzymes in muscle tissue compared to healthy subjects [229]. Investigations by FRONTERA et al. in elderly healthy men showed the following changes after 12 weeks of strength training: 28% increase in muscle mass, 15% increase in capillary and muscle fibre, 38% increase in citratsynthetasis activity [230]. The lactate behaviour in this study confirms these findings, as a change in the lactate kinetics (right shift) was found in the intervention group. This means an increase in endurance by an improved aerobic energy supply. Our findings underline the fact that the deficient muscular system in COPD is the limiting factor rather than the cardiovascular system.

COPD patients can develop their endurance performance positively on the basis of increased muscle strength. Thus, general physical performance could probably be improved quicker by muscle strength exercises than by endurance training in this population. For instance LEUPPI et al. only found an increase of 13.2W in maximal ergometry workload after a 4-month endurance training intervention in patients with moderate COPD [231].

The high intensity resistance training induced increases in physical exercise capacity that were also reflected in improved general well-being by an increase in the health-related quality of life (HRQL), evaluated by the SGRQ - although a short-term decline of the HRQL was observed in the intervention group in the first 4 weeks. The explanation for this might be that the training intervention was a new stress factor at first, but then the patients slowly got accustomed to the training process. Thus, a significant increase in the HRQL was observed in this group from test 1 to 4, whereas the control group showed a trend of declining HRQL over the same period of time. Several factors might be responsible for the positive changes in the treatment group: increased physical capacity, improved body perception as well as increased social contacts, which were cultivated again in the training group during the therapy process. The sum of these effects

probably led to a better accomplishment of daily life requirements and promoted the social reintegration of the COPD patients.

The results of the BDI questionnaire, presented this cohort of 28 COPD patients with a significantly higher score of 11.29 compared to a healthy population which is referenced with a score of 6.45 [227]. COPD patients are therefore closer to psychosomatic pain patients who usually achieve a mean value of 11.4 in depression symptoms. However, the population of depression patients are referenced with a much higher score of 23.7 [227] which are double of what this COPD cohort achieved. Nevertheless, depressive symptoms should be considered in the overall context of comorbidities in COPD patients.

The introductory question—whether high intensity hypertrophic strength training influences respiratory function, health-related quality of life, and endurance performance of COPD patients—can be answered positively. All parameters showed significant improvements in the intervention group (STG), except in peak flow performance, where only a tendentious increase was found.

Therefore, the applied training programme seems a sensible addition to the common therapy practice. Regarding the specific requirements for an effective COPD exercise therapy, resistance training has a spectrum of advantages that cover – muscle hypertrophy, improved aerobic performance, not provoking dyspnoea as much as endurance exercises do and possibly a more specific effect on hormonal deficits. Resistance training generally causes a greater increase in testosterone than endurance training [226]. Another advantage might be that strength training is more likely to be better tolerated by these patients because of the intermittent nature of the exercise. Even patients with severe COPD are able to carry out an intensive training lasting up to 2 hours. This provokes a stronger disturbance in homeostasis, which in return initiates appropriate structure-developing anabolic biological responses, whereas experience has shown that COPD patients are usually struggling when undergoing longer endurance training exercises because of increased dyspnoea and muscular fatigue.

CONCLUSION

From the results of this study into the effects of high intensity strength training with COPD patients, it can be concluded that a 12 week high-intensity strength training programme is suitable to improve pulmonary function and performance measurements of patients with moderate to severe COPD. These changes lead to an improved health related quality of life. Furthermore, the data showed that

COPD patients have significantly more symptoms of depression than a healthy population. The level of depression is similar to those of psychosomatic pain patients. The conclusion can be drawn that high intensity resistance training is preferable for a COPD-specific exercise therapy and offers new treatment perspectives – especially for severe cases of COPD as the intermittent structure of strength training suits the disease specific symptoms of COPD patients better, as they are usually struggling when undergoing longer endurance exercises because of increased dyspnoea and muscular fatigue.

5 COPD STUDY 2

Effects of an Inspiratory Muscle Training (IMT) versus a Conventional Exercise Therapy on Respiratory Function and Functional Exercise Capacity in COPD Patients.

5.1 Objectives

COPD patients usually present an expiratory flow limitation, causing dynamic hyperinflation during exercise with a consequent reduction in inspiratory capacity. This aspect is limiting their exercise tolerance. The exercise capacity of COPD patients with tidal expiratory flow limitation at rest, therefore, depend on the magnitude of inspiratory capacity [231].
Thus, inspiratory strength training (IMT) presents an interesting area of research in the context of additional therapeutic options in the treatment of COPD.

However, the role of IMT for patients with stable COPD is unclear [232]. Neither the American Thoracic Society nor the European Respiratory Society standards, recommend the inclusion of IMT into the disease management plan of COPD [233]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2010) states that "respiratory muscle training is beneficial, especially when combined with general exercise training" based on non-randomised trials and observational studies.

The American College of Chest Physicians and AACVPR (ACCP) decided recently to update prior topics and recommendations and to review new topics. One of the additional topics was IMT and similar recommendations were given as by GOLD – concluding that IMT is beneficial when applied in conjunction with exercise therapy [234].

The latest meta-analysis regarding IMT was conducted by GOSSELING et al. (2011) which included 32 randomised controlled trials on the effects of IMT in COPD patients [235]. The analysis proved significant improvements in maximal inspiratory muscle strength (PI_{max} +13 cmH_2O), endurance time (+261s), 6- or 12-min walking distance (+32 and +85m respectively) and HRQL (+3.8 units). Dyspnoea was significantly reduced (Borg score -0.9 point; Transitional Dyspnoea Index +2.8 units) and endurance exercise performance tended to improve, while no effects on maximal exercise capacity were found. However, respiratory muscle endurance training revealed no significant effect on PI_{max},

functional exercise capacity and dyspnoea [235]. The authors came to the same conclusions as ACCP, AAVCPR and GOLD that the addition of IMT to a general exercise training programme improves PI_{max} and tends to improve exercise performance and therefore can be understood as a useful add on tool for the rehabilitation of COPD patients.

However, all the aforementioned studies investigated the effects of IMT in a longer term outpatient setting, but not the short term effects of IMT in a hospital rehabilitation setting with hospitalisation durations of only 3 to 5 weeks. This novel approach is relevant as the very short intervention time limits the physiological adaptations that can be achieved during hospitalisation and therefore also affects the patients' ability to perform activities of daily living (ADL) after being discharged.

This study therefore investigated the following hypotheses:

1. IMT in combination with conventional exercise therapy can improve respiratory function in COPD patients.
2. A three week IMT has positive effects on respiratory muscle strength in COPD patients.
3. IMT has additional positive effects on endurance performance in COPD patients.
4. An additional IMT has positive effect on the HRQL of COPD patients.
5. There is a correlation between improved exercise capacity and HRQL.

5.2 Methods

5.2.1 Subjects

A total of 73 COPD patients (GOLD stages I-IV) were recruited from patients who were admitted to the Pulmonary Rehabilitation Clinic Heiligendamm, Germany (part of the Median Company). They were allocated by the assessing physician to a conventional exercise therapy group which was treated as a comparison group (CPG) (n=37) and an intervention group (IMTG) (n=36) that underwent the conventional exercise therapy plus an additional IMT five times a week. The patients therefore were not randomised as the medical personnel wanted to gain a maximum benefit for their patients by allocating more severe patients to the IMT intervention group as it was hypothesised that COPD stages III and IV would probably benefit most from the additional therapy. For this reason a homogenous sub-group was created when analysing the data – see table 25.

The overall cohort consisted of 31 men and 42 women whose distribution according to the GOLD stages were – I: n=3; II: n=29; III: n=29; IV: n=17. The average age of this cohort was 62±8.98 years with an average BMI of 27.5±5.96 and a mean FEV_1 of 49.0±20.14. For ethical reasons it was not possible to create a control group with no exercise intervention at all as the physical rehabilitation is an accepted part of the disease management programme of COPD and therefore any national and international guidelines.

Because of the heterogeneity of the groups the cohort was then stratified according to their severity stages in order to allow a valid comparison and correlation data analysis of both groups regarding HRQL and exercise capacity. Although all patients completed the study the respective data only refers to 44 patients (intervention group n=21, comparison group n=23) of who 24 were men and 20 women. Table 25 presents the anthropometric and respiratory details of this sub-cohort.

Table 25: Specifications of the patients in the stratified sub-cohort - intervention and comparison group (n=44).

Age (years)	61.7 ± 9.0
Height (m)	170.0 ± 0.1
Weight (kg)	78.8 ± 16.2
Body Mass Index (kg/m^2)	27.2 ± 5.5
GOLD-classification	2.7 ± 0.8
FEV_1 (%)	49.7 ± 21.0

Declaration of Consent:
All subjects had to sign a declaration of consent before being considered for one of the study groups. The patients received information in writing about the overall study design, the specific intervention and benefits and risks associated with it. Furthermore, a personal interview was held by a physician. There was no need for approval by an ethics committee as only established therapy methods were used in this study and the only difference to the standard therapy of the hospital was the IMT intervention.

Study Termination:
Every patient could terminate the study at any time.

Inclusion Criteria:
- $\geq$ 18 years
- Women and men
- COPD diagnoses after broncho-spasmolyses test
- Clinical COPD stage according to GOLD: II-IV
- Diffusion capacity and/or manifest partial insufficiency <70%
- The patient was cleared for participating in this study by a physician considering comorbidities such as CHD, hypertension, osteoporosis, depression etc.
- 3-4 weeks hospitalisation
- The patient's declaration of consent to participate in the study

Exclusion Criteria:

- COPD exacerbation
- Symptomatic CHD
- Malign CHD
- Severe osteoporosis
- Severe obesity (BMI > 35)
- Untreated arterial hypertension
- Pulmonary hypertension (pulmonary-arterial mean pressure >20mmHg)
- Decompensated heart failure
- Acute infections
- Instable asthma
- Haemodynamic affective arrhythmias
- Global respiratory insufficiency

5.2.2 Experimental Procedures

Study Design

TEST PROCEDURES

The test profile was applied at two points – at baseline and shortly before being discharged from hospital after a therapy duration of three weeks. The test profile of the baseline and final retest included the following procedures: clinical examination by a pneumologist including a respiratory function test as well as further tests conducted by an exercise therapist: 6-Minute-Walk-Test (6MWT), health related quality of life questionnaire (CRQ), bio-impedance analysis and a strength test (12-RM).

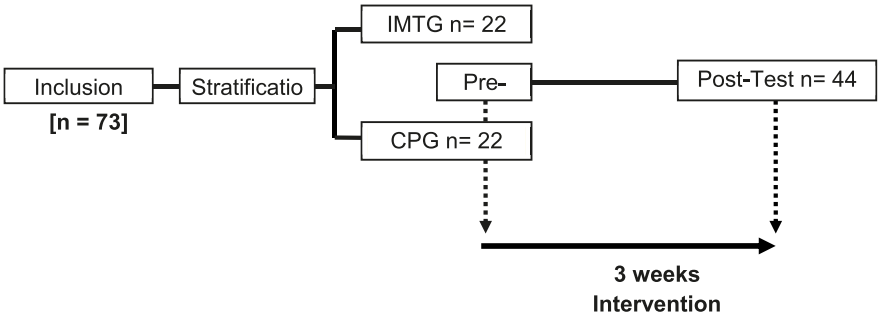

Figure 37: Schematic Study Design.

INTERVENTIONS

The general therapy scheme included an educational module (contents according to COPD DMPs), psychotherapy, a dietary advice/nutrition module, smoking cessation and exercise therapy - three times weekly. The latter consisted of strength training (hypertrophy method, followed by strength endurance), endurance training (20-30min continuous method), breathing therapy and ball games. The intervention group (IMTG) completed an inspiratory muscle training five times a week in addition to the usual three exercise sessions.

The IMT was conducted from Monday to Friday from 0845 until 1100 hrs. and took no longer than 30min for each patient. The first part of each session focused on strength development of the respiratory muscles (high intensity) and the second part focused on muscle endurance (low intensity). Also, the day by day individual inspiratory respiratory performance was tested at the beginning of each session. For a detailed intervention description see table 26.

Table 26: Inspiratory exercise regime of the intervention group (IMTG).

Training Phase	Contents
Educational Phase: Induction	Formal induction into the use of the IMT Respifit device by qualified personnel and an inspiratory muscle strength baseline test to identify individual training values .
Phase 1: Test	Inspiratory test to determine Pi_{max} 80%.
Phase 2: Strength	6-15 reps. of maximal expiration followed by short powerful inspiration against a resistance produced by the device. 30s pause between each repetition.
Phase 3: Muscle endurance	6-12 sets each of 1min duration at 60% Pi_{max} with a 30s pause in between.

EQUIPMENT

Spirography/ Bodyplethysmograph (BODY)

The pulmonary function measurements were carried out in all tests with the Bodyscope device (GANSHORN Medizin Elektronik, Niederlauer, Germany) at the same time under standardised conditions. Among other variables, the forced expiratory ventilation in 1 s and the flow resistance were measured. See picture below.

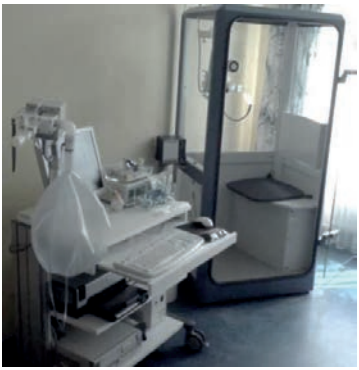

Figure 38: The Bodyscope Bodyplethysmograph. (own source)

IMT Training

The inspiratory muscle training was conducted with the Respifit S device (BIEGLER, Mauerbach, Germany. The training equipment consists of the actual housing, a screen and a chipcard for each individual patient storing the data. Other external parts were the nose bracket and a mouth piece. See figure 40.

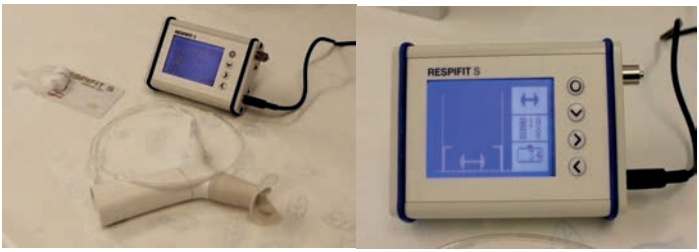

Figure 39: Respifit S - the IMT intervention device. (own source)

Health Related Quality of Life (HRQL) Questionnaire

For measuring the health-related quality of life, the *Chronic Respiratory Questionnaire* (CRQ) was used. This questionnaire is a standardised and validated tool similar to the St. Georges' Respiratory Questionnaire and in comparative studies no significant difference was demonstrated between the two. The advantage of the CRQ is the reasonable price compared to the SGRQ. According to GUYATT (2009) a change of 0.5 units in the CRQ overall scoring is clinically relevant [236].

6-Minute-Walk-Test (6MWT)

The 6MWT is an objective testing tool to determine the patients' ADL performance and/or functional submaximal exercise capacity. The objective is to walk as long a distance as possible within 6 minutes without running. One of the hospital's corridors is 50m long and was ideal for conducting this test. The 6MWT was always done at the same time between 0900 and 1100 from Monday to Friday. The patients were walking in their own pace, one at a time. Crutches or other walking aids were generally permitted. The pauses if necessary had to be kept as short as possible. The patients received standardised instructions by the test supervisor and were encouraged verbally every 30s by phrases like "you are doing well" or "come on – you can do it". The covered distance was finally added to make up the overall result.

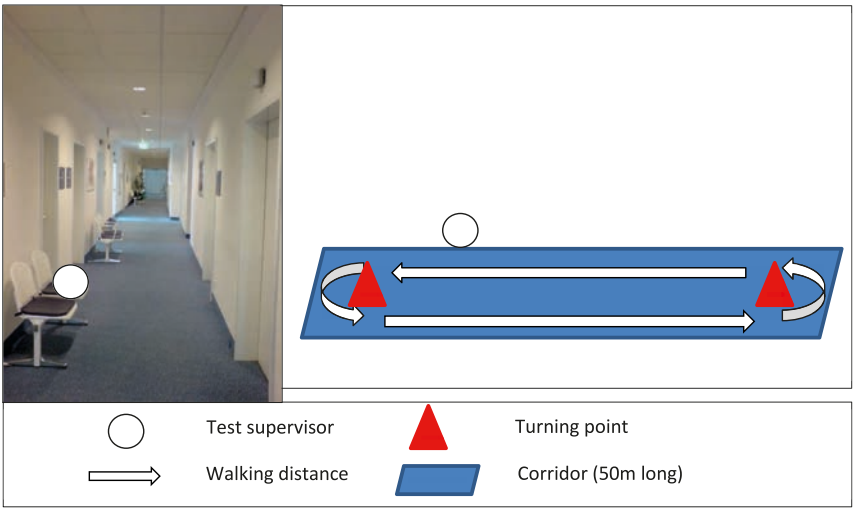

Figure 40: Illustration of the 6MWT.

Strength Test Equipment

The Legpress and Latpull equipment of the rehabilitation line of the company SVG (Ötisheim, Germany) were used. See figures 42. Both devices enabled the patients to sit in an upright position which is important for COPD patients in order to avoid any unnecessary dyspnoea.

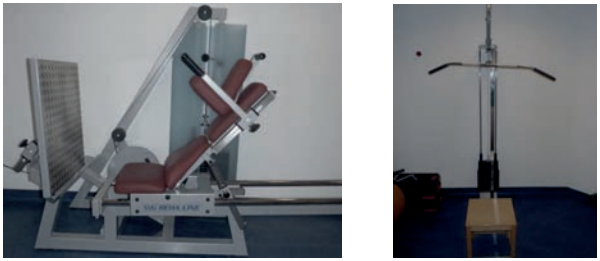

Figure 41: Legpress and Latpull.

Other Training Devices

The strength training equipment was made up of training machines using weight plates for resistance (SVG Medizinsysteme, Ötisheim, Germany). The machines enabled the patients to train all major muscle groups. The endurance training was either carried out as a walking exercise or on a stationary bike.

5.2.3 Statistics

The data was firstly tested for normal distribution by means of the *Shapiro-Wilk-Test*. A normal distribution was not confirmed and therefore a *Man Witney U-Test* was applied for unpaired samples and the Wilcoxon-Test for paired samples. For the homogenised group (n=44) the *Levene-Test/ANOVA-Test* was used. The correlation analysis was conducted by means of *Spearmann-Rho*. P-values of <0.05 were considered significant. The data was analysed according to the *Per-Protocol* procedure.

5.3 Results

Respiratory Function: FEV_1, FVC_{in}, FEV_1/VC_{in}, RV/TLC

Table 27 presents the pulmonary function data of the intervention group pre and post the three week IMT intervention. The measurements show a significant increase in FEV_1 (p=0.04) from 37.91 ±15.25% in the baseline test to 40.66±15.58%. All other parameters presented no significant changes.

Table 27: Respiratory function tests in the intervention group (IMTG) (n=22).

Parameter	Mean value ±SD Pre	Mean value ±SD Post	p-value	Significance
FEV_1 (%)	37.91 ±15.25	40.66 ±15.58	0.04	significant
FVC_{in} (%)	63.53 ±16.44	66.16 ±13.49	0.196	n.s.
$FEV1/VC_{in}$ (%)	62.94 ±23.21	61. 59 ±15.84	0.553	n.s.
RV/TLC (%)	167.41 ±23.87	164.88 ±25.49	0.352	n.s.

Table 28 shows the pre to post intervention mean values of the respiratory measurements of the comparison group. No significant changes could be demonstrated.

Table 28: Respiratory function tests in the comparison group (CPG) (n=22).

Parameter	Mean value ±SD Pre	Mean value ±SD Post	p-value	Significance
FEV_1 (%)	58.22 ±19.4	60.89 ±18.97	0.172	n.s.
FVC_{in} (%)	78.19 ±18.26	79.08 ±16.71	0.671	n.s.
$FEV1/VC_{in}$ (%)	74.86 ±18.48	76.95 ±19.04	0.056	n.s.
RV/TLC (%)	140.78 ±25.91	136.70 ±26.51	0.227	n.s.

The results of the respiratory measurements of both groups were compared by using the *ANOVA* analysis and could not prove any significant differences between the intervention and the comparison group.

Respiratory Function: *Respiratory Muscle Strength*

The intervention group (IMTG) improved their maximal inspiratory pressure (Pimax) significantly. Pimax increased from 5.34 ±1.99 kPa at baseline to 6.38 ±1.65 kPa after the intervention. In the comparison group (CPG) no significant changes were found. See table 5 for details.

Table 29: Results of the maximal inspiratory pressure test in both groups.

Group	Parameter	Mean value ±SD Pre	Mean value ±SD Post	p-value	Significance
IMTG	**Pimax (kPa)**	5.34 ± 1.99	6.38 ± 1.65	0.002	Significant
CPG	**Pimax (kPa)**	7.87 ± 2.79	8.33 ± 3.69	0.137	n.s.

The comparative results of the maximal inspiratory pressure measurements of both groups using the ANOVA analysis showed that there was no significant difference between the intervention and the comparison group.

Respiratory Function: ***Respiratory Muscle Strength Respifit S***

The changes in respiratory muscle strength in the intervention group show a significant increase (p=0.00) from pre to post test: from 47.39 ±20.1 to 68.55 ±22.85. The respiratory minute volume also improved significantly from 6.5 ±2.83 to 8.09 ±3.33 (p=0.00) as presented in figure 43.

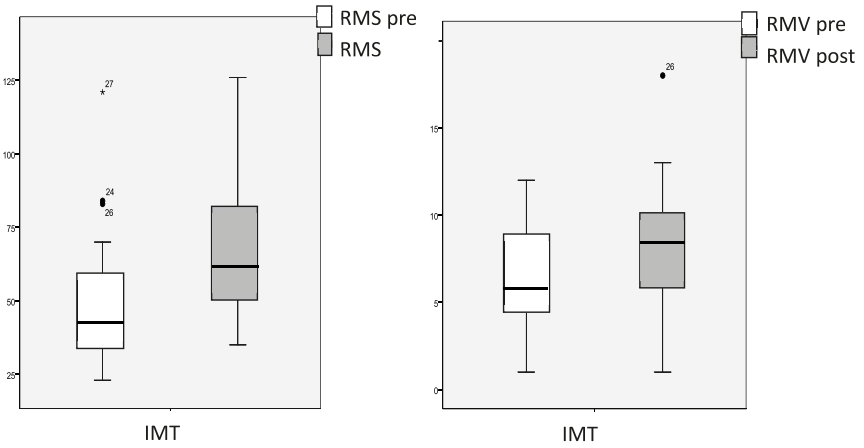

Figure 42: Results of the respiratory muscle strength (RMS) (left) and respiratory minute volume (RMV) (right) in the intervention group.

Functional Exercise Capacity: ***Walking distance and strength***

The intervention group (IMTG) was able to improve their walking distance in the 6MWT from baseline to retest after 3 weeks of exercise therapy and IMT significantly from 409.1 ±125.7 to 452.27 ±117.7 which equates to an increase of 43.2 ±126.0m (p<0.01) – expressed in percentages 11%. The comparison group (CPG) also showed significant results – however, only walking 17.1 ±63.7m farther than the 444.8 ±115.6m at baseline (p<0.01) which equates to only 4%. Although the difference in distance is with 26.1m and a p-value of p=0.39 not significant, the intervention group still presents a 7% higher increase than the comparison group.

The improvements in strength performance were also significant in both groups. The intervention group increasing their strength in the Leg-press

exercise from 75.1 ±28.4 to 88.6 ±23.5 by 13.4 ±11.5Kg ($p<0.01$) which equates to 18% improvement while the comparison group had an increase of 17% (17.5 ±16.5Kg). The differences in the upper extremities tested by the Lat-pull exercise also showed significant improvements in both groups – in the intervention group by 25% (4.2 ±3.8Kg) from 16.8Kg to 21.1Kg and in the comparison group by 19% (4.0 ±3.4Kg) from 21.2Kg to 25.3Kg ($p<0.01$) as presented in table 29.

Table 30: Increases from pre- to post-test in the intervention (IMTG) and comparison group (CPG) (n=44).

Parameter	Group	n	Mean value	SD	p-value
Walking distance (m)	Intervention	22	43.18	126.0	0.00
	Comparison	22	17.05	63.1	0.00
Strength lower extremities (Kg)	Intervention	22	13.40	11.53	0.00
	Comparison	22	17.50	16.49	0.00
Strength upper extremities (Kg)	Intervention	22	4.22	3.80	0.00
	Comparison	22	4.04	3.41	0.00

Comparing the improvements in both groups against each other by applying the *Levene-Test*, no significant difference could be demonstrated.

Health Related Quality of Life (HRQL)

The 3-week rehabilitation programme led in all subjects of the cohort (n=44) to significant improvements of the HRQL ($p<0.05$) measured by the CRQ. The clinically relevant increase of over 0.5 point units showed a range 0.67 (minimum) to 2.1 (maximum) and therefore proves a relevant effect.

In figure 44 the intervention group showed significantly higher scores in the items *Mastery* and *Emotional Function* and tendentious better results in the overall score and the item *Fatigue* whereas the comparison group had a slightly higher score in the *Dyspnoea* item, but statistically not significant.

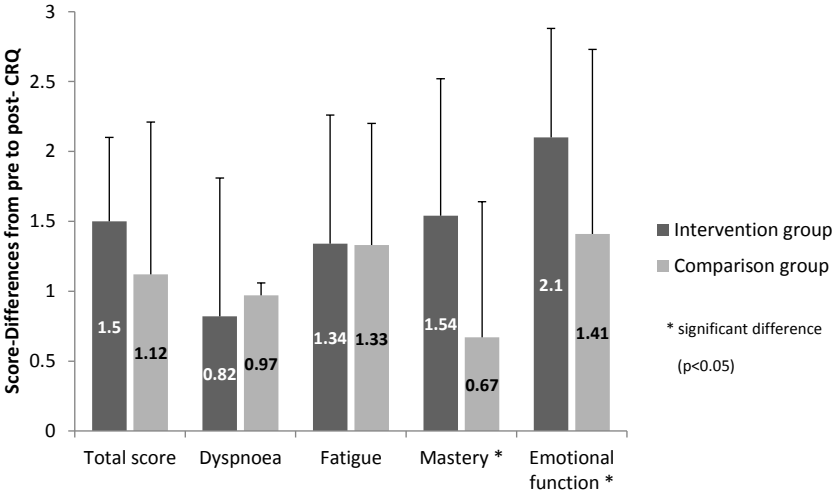

Figure 43: Improvements of the intervention and control group in HRQL measured by the CRQ (n=44).

Correlation of exercise capacity and HRQL

The intervention group showed no significant correlation between any of the three physical parameters (6MWT, strength tests lower extremities and upper extremities) and the HRQL. Only the comparison group presented a significant correlation between the scores in the CRQ and the 6MWT (p=0.04) – see table 30.

Table 31: Correlation analysis in the comparison group using the *Spearman-Rho-Test*.

Test	Correlation coefficient	p-value
Strength: Latpull	0.38	0.22
Strength: Legpress	-0.12	0.71
6MWT	0.60	0.04 *

* significant

5.4 Discussion

According to GEDDES et al. (2008) it is important in pulmonary rehabilitation to use IMT in combination with other interventions [232]. However, there are no established thresholds for what constitutes a clinically relevant change in inspiratory muscle strength or in endurance, other methods must be utilised to infer clinical benefit [237].

This study only found a significant improvement in respiratory function in the FEV_1 in the intervention group (IMT) which confirms, to some extent, the effectiveness of IMT. However, it needs to be considered that these results were produced during only three weeks of hospitalisation while all other studies were conducted in an outpatient setting with much longer intervention duration. The respiratory strength also increased, as expected, significantly in the IMT group ($p<0.01$). These results were also confirmed by the same group, regarding the respiratory strength and respiratory minute volume using the training device Respifit S ($p<0.01$). However, POLKEY and MOXHAM (2004) mention that maximal inspiratory pressure is a volitional test and therefore open to criticism which should be considered when discussing these results [238].

GEDDES et al. (2005) recommended a similar training frequency, as in this study, of at least 30 minutes daily but also point out that this time can be spread over more than one session a day. Training should occur at least 5 days a week [239]. Although this study also used an IMT protocol of five days a week, the actual training duration was no longer than 30 min – however, this still proved effective to produce the above increases in respiratory function. GEDDES et al. also state that gains caused by physical exercise may be measurable after as short as 5 weeks in COPD patients and IMT should also become part of the patients' exercise programme. The results of this study do not necessarily contradict these recommendations, but at least seem to relativize the timeline in which effects by IMT can be achieved – in this case as short as 3 weeks. Similar to the results presented in this study, LOTTERS et al. (2002) also found that IMT can significantly increase inspiratory muscle strength and inspiratory muscle endurance [240]. Additionally the same author found in his review, a clinically significant decrease in dyspnoea sensation at rest and during exercise after IMT [240]. However, this cannot be confirmed by this study. Only the comparison group showed a non-significant improvement in the dyspnoea item of the CRQ.

Regardless of the effects of IMT, this study confirms the effectiveness of a three week hospitalised rehabilitation programme. This cohort of COPD patients (n=44) showed significant increases in all components of exercise ($p \leq 0.01$) ranging from 11% improved endurance to 25% strength increases. Similar clinically relevant results were produced concerning the HRQL. The intervention group (IMTG) scored significantly higher in the items *mastery* and *emotional function* compared to the comparison group (CPG). However, these results should be confirmed by other studies investigating the effects of IMT in a hospital setting – ideally for more than 3 weeks.

CONCLUSION

In conclusion, it can be said that IMT in addition to conventional exercise therapy improves FEV_1 as well as inspiratory muscle strength and endurance, functional exercise capacity (6MWT) and health related quality of life. However, further research is needed to explore the impact that different training protocols may have on outcomes as well as different intervention times during common hospitalisation durations, i.e. 3 weeks vs. 4 vs. 5 weeks. According to GEDDES (2008) the extent to which changes in outcomes associated with IMT translate into clinically important improvement for adults with COPD, also needs to be determined [232].

6 DISCUSSION

The coexistence of cardiac and pulmonary disease has risen dramatically over the past three decades. Many patients, who present a significant cardio-vascular disease such as chronic heart failure, also suffer from a pulmonary disease. COPD is therefore a frequent co-morbidity in CHF, and the prevalence ranges between 20 and 30% [241,242,243]. COPD patients in return have a markedly elevated risk of heart failure and COPD is a strong and independent risk factor for cardiovascular morbidity and mortality. Co-existing COPD further worsens prognosis in CHF patients [244]. It therefore appears to be a logical consequence to investigate the effects of exercise interventions in both conditions in conjunction with a similar exercise therapy approach/concept – especially as the pathophysiology and symptoms of both conditions are very similar.

CHF/COPD – SIMILAR PATHOPHYSIOLOGY AND SYMPTOMS

Chronic Heart Failure and Chronic Obstructive Pulmonary Disease have a range of physiological and psychological aspects in common which are relevant for the disease management of both conditions as presented earlier in this work. Although CHF is defined as a complex of symptoms that is related to the inadequate perfusion of tissue during exertion and COPD as a lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible, the non-cardiac and non-pulmonary factors are very similar in both conditions such as neurohormonal changes, muscle atrophy, muscle fibre shift and others that independently can cause dyspnoea, fatigue, and oedema that are characteristic of the clinical syndrome of CHF [245,246] and COPD. These pathophysiological changes are even interrelated to a certain extent when looking at the pathogenesis of right ventricular dysfunction (diastolic heart failure) which is usually caused by pulmonary hypertension which in return can be a physiological consequence of COPD.

In both diseases the so called vicious cycle plays a key role which is mainly characterised by an increase of symptoms during physical activity, therefore the patient avoids physical activity and this initiates de-conditioning processes which lead to a further loss of functional capacity on all levels and an increase of cardiac and pulmonary symptoms [247,248,249,250]. The focus of research therefore lies in understanding the systemic effects of both conditions with a chain of catabolic events caused by inflammatory processes, hypoxia and disuse which are expressed in muscle wasting and muscle fibre shift towards anaerobic muscle

fibres. In COPD and CHF, the failure to provide peripheral tissues with sufficient amounts of oxygen is accompanied by similar maladaptive responses that may lead to an anabolic-catabolic imbalance with the development of cardiac cachexia. The deficiencies or resistance to growth hormone and testosterone also plays an important role in the pathophysiology of both conditions as addressed in COPD study 1 where testosterone was measured and a chain of arguments was built around the catabolic state of COPD patients and heart failure patients in the CHF study respectively. The enhanced catabolic status is therefore significantly associated with exercise intolerance, ventilatory inefficiency, and chronotropic incompetence in these patients, suggesting a significant contributing mechanism to their limited functional status [251,252]. These circumstances drive the catabolic processes of muscle atrophy and change in muscle fibre composition - especially in the fatigue resistance slow twitch type 1 fibres [253,254]. Parallel to this loss in type I fibres, a significant increase of type IIX fibres was found in COPD patients [254] and of type 2A fibres in CHF patients respectively [255].

Due to the aforementioned common systemic symptoms in CHF and COPD a symptom specific intervention should be applied to treat these two conditions adequately. Both conditions are so similar from a rehabilitation/sports medicine point of view that it seems a logical consequence to investigate specific exercise interventions for CHF and COPD in conjunction and also to develop rehabilitative structures where both patient groups can be treated together in one exercise setting. The aforementioned specific maladaptation was acknowledged by the applied exercise regimes in all three studies.

In this context resistance and/or strength training should be especially considered as it seems to meet the demands of these conditions perfectly because of its symptom-specific anabolic effects (low testosterone and IGF1 levels) and a better toleration by the patients because of the intermittent nature of the exercise which can prevent or at least reduce dyspnoea and general discomfort during the exercise therapy and thereby possibly increase the compliance of patients to exercise.

TWO CONDITIONS – ONE EXERCISE THERAPY

The similarities in limiting factors of exercise tolerance in CHF and COPD lead to the conclusion that the same exercise interventions in both populations should be applied. In the focus of attention stands the catabolic state of the patients and their consequences in the form of muscle wasting as well as severe dyspnoea during exercise which reduces their compliance to exercise. The requirements for

a suitable exercise regime for both conditions therefore include an exercise that allows long enough training sessions to initiate anabolic responses without causing severe dyspnoea as well as specifically compensating muscle wasting.

MAIORANA et al. (2000) confirms that exercise training programmes aimed at improving exercise capacity in patients with CHF should be designed to specifically target the limitations of functional capacity in these patients [256]. A great number of previous controlled trials have demonstrated beneficial effects of exercise training, but the majority of these utilised prolonged, repetitive, dynamic aerobic modalities that are often poorly tolerated due to the onset of dyspnoea and localised muscle fatigue in both populations CHF and COPD. Other exercise prescriptions, specifically targeting the systemic and peripheral abnormalities present in heart failure and/or COPD have been investigated, but only in smaller trials and also not differentiating between different strength training methods in the same study.

The increase in muscular strength through the use of resistance training in rehabilitative exercise interventions in CHF and COPD is also of clinical relevance – especially considering activities of daily living (ADL) and mobility and therefore an independent life. As aforementioned, both patient populations exhibit skeletal muscle atrophy and impaired muscular strength.

This has important implications for the patient's capacity to perform tasks of daily living, many of which are dependent on muscular strength and indicates that strength training interventions whether circuit training or high intensity hypertrophy training are an effective modality for improving peripheral muscle function in addition to cardiovascular performance (VO_{2peak}).

PHYSIOLOGICAL ASPECTS OF EXERCISE THERAPY

CHF

Endurance/VO_{2peak}

One way to demonstrate these positive training adaptations regarding the performance and exercise tolerance of patients are therefore changes in Peak VO_2, which has been shown to increase with mean values between 11.5% and 29% in CHF patients [251,252,253,254,255]. The results in the presented CHF study showed even greater improvements in VO_{2peak} in all exercise groups between 24% and 53% compared to the comparison group (non-training/dietary group) with 5% of the baseline measurement. Surprisingly the high intensity strength training

group showed the greatest increase with 53% ($p<0.01$). This underlines the significance of muscular strength in endurance exercises as well as a possible muscle fibre shift to increased numbers of type 1 oxidative fibres which has been proven in healthy subjects undergoing a high intensity strength training. These results are similar to findings of GIALLAURIA et al. (2008) [211] with an increase of Peak VO_2 by 31%, the same improvements as in the study of CALLAERTS-VEGH et al. (1998) [212] and DEMPOULOS et al. (1997) [213] (+30%).

Other publications have demonstrated that the maximal workload in the cycle ergometery can increase through exercise interventions in heart failure patients by an average of 15 to 32 Watts as well as the exercise duration of 12-45% and longer walking distances of 16% to 65% [204,205,207,208,209,210], but all of the above studies used primarily endurance exercises as an intervention, which were predominantly carried out using a cycle ergometer. Whereas, only very few studies used strength training interventions. The latter showed changes in maximal strength by a mean increase of 28% [204,205], but also a positive change of VO_{2max} and the overall performance in the cycle ergometry [204]. This also applies to all of the presented CHF and COPD studies, which can be explained when considering the catabolic situation of any chronic internal disease and especially of CHF patients.

NT-pro-BNP

Another parameter relevant for any cardiac population is the *N-Terminal Prohormone of Brain Natriuretic Peptide* or short NT-pro-BNP. NT-pro-BNP is an amino acid fragment which is used for screening and diagnosis of CHF. It is also being discussed for the use of establishing prognosis in heart failure as NT-pro-BNP is a marker that is typically higher in patients with worse outcome. Thus, the effect of exercise on this parameter is extremely relevant next to the Ejection Fraction (EF) and the Left-Ventricular-End-Diastolic-Diameter (LVEDD). Some studies have shown a significant decrease of the NT-pro-BNP caused by a combined strength and endurance training in NYHA III-IV patients (from 2428pg ml^{-1} down to 1900pg ml^{-1}) [250,254]. A recent review by SMART and STEELE (2010) that included 9 studies found that exercise training significantly lowered NT-pro-BNP (mean difference of -621pg/mL, 95% confidence interval -844 to -398, I2=75%; six studies), although a significant heterogeneity was noted. However, sensitivity analysis showed that changes in NT-pro-BNP remained statistically significant [257].

The effects of different exercise interventions on the parameter NT-pro-BNP showed in our CHF study a significant reduction ($p<0.01$) in the endurance-

training-group (ETG) from 1495±1555pg/mL down to 934±702pg/mL, the other groups also demonstrated reductions in NT-pro-BNP – however, these were not significant. The circuit-training-group (CTG) presented a decrease from 2115±1880pg/mL to 1602±1772pg/mL. Although a mean difference of 613pg/mL appears to be huge, the SD does not allow for a significant effect. The high intensity strength-training-group (STG) showed a reduction in this parameter from 1333±1498pg/mL to 1078±1351pg/mL and the comparison non-training-group (CPG) with a dietary and educational intervention in accordance with disease management standards had a change from 1557±907 pg/mL to 1248±794pg/mL. These partially non-significant effects stand in contrast to other parameters such as the EF and LVEDD.

EF and LVEDD

The ejection fraction showed significant effects ($p<0.01$) from pre to post tests in all exercise groups, but not in the comparison group. The ETG presented an increase by 15% (from 31±6 to 46±8%), the CTG showed the highest increase with 16% (from 29±7 to 45±11%) and the STG had improved by 15% (from 30±7 to 45±7%), while the CPG only showed a non-significant change of 2% (from 33±8 to 34±6%). This proves the effectiveness of systematic and progressive exercise interventions in general on cardiac function. The parameter LVEDD also presented a similar behaviour whereby all exercise groups had significant improvement from pre to post test ($p<0.01$), but not the comparison group. These improvements showed in a reduction in diameter of the left ventricle – the ETG had a reduction of 4mm (from 59±8 to 55±8mm), the CTG of 6mm (from 63±9 to 57±7mm) and the STG presented the greatest reduction with 7mm (from 63±9 to 56±6mm) whereas the CPG only showed a decrease in diameter by 2mm (from 62±8 to 60±5mm). Whether this different behaviour of NT-pro-BNP to EF and LVEDD is a coincidence in this study or is a general characteristic of endurance training and/or strength training interventions cannot be answered by this study, but needs to be investigated by future research.

The above results of improvements in EF and LVEDD also reflect in the changes of NYHA-classification where all the CHF-patients in this study improved by a whole class. These significant improvements ranged from -39% to -47% compared to the CPG with -16% of the baseline measurement, whereby the CTG and the STG showed again the greatest increase with -42% and -47% ($p<0.01$). The above changes are especially remarkable as all patients received an optimised medication scheme according to the European Society for Cardiology before any other intervention was introduced and this scheme was not altered in any way

throughout the duration of the study. It also needs to be emphasised that all cardiac parameters that required measurements by a cardiologist for analysis were conducted by an independent cardiologist who was not involved in the study and only received the blinded ultrasound images for analysis of EF and LVEDD of the study cohort. Any biased measurements/analysis was thereby avoided.
These results are coherent with the changes in the EF and prove the significance of catabolic changes caused by CHF including neurohormonal and muscular maladaptation and the role of strength training in this context. Some studies showed an increase of EF by 6.3% and an improvement of the stroke volume by 27% and at the same time a significant reduction of the LVEDD [198,202,207,209]. This is unlike the huge unexpected changes in the EF of the cohort in our study with a relative mean increase by 50% to 66% in all exercise groups compared to the CPG, which had an improvement of only 11%. The ETG showed an increase of 50% ($p<0.05$ vs. CPG) and the CTG with 66% and the STG with 61% (both $p<0.01$ vs. CPG).

A study conducted by KELLERMAN et al. (1990) using a high intensity arm ergometry exercise (90% maximal performance) also showed a remarkable increase of the EF by 40% (increasing from 30.1% ±9.5 to 42 ±12.2 in 36 months). The same study demonstrated an increase of peak power from initially 43.5 ±15.2 Watt to 62.5 ±13.3 (+44%) [216]. The findings of this study are also confirmed by a review by BRAITH and BECK (2008). This publication presents evidence that improvement of skeletal muscle phenotype (muscle mass, fibre morphology, and histochemistry) should be a fundamental goal of rehabilitation in patients with CHF. Moreover, strength training may be the preferred exercise modality when targeting the peripheral muscle adaptation [217] or at least should be added to an endurance exercise regime in CHF patients.

Strength

The increases in strength performance were naturally higher in all the training groups and as expected the highest strength gains were achieved in the STG and CTG ($p<0.01$), but even the ETG showed significant changes. These are predominantly caused by the high proportion of strength necessary for the leg work and partially to stabilise the upper body (arms etc.).

Traditionally, strength exercise has been avoided in CHF and COPD because of fears that it may increase the haemodynamic stress over an acceptable level, decrease myocardial perfusion and/or provoke arrhythmias [258]. Blood pressure behaviour during exercise was also one of the parameters in this CHF study.

MCKELVIE et al. (1995) compared haemodynamic responses to both strength exercise and continuous aerobic exercise (cycling) of similar relative intensities as one of the parameters investigated. The outcome was that the resistance modality was associated with favourable responses [259].

Blood Pressure

The results show that the maximum systolic value during a high intensity strength training only reached 151.1±mmHg and during circuit training 193.3±5.1 mmHg which was probably due to the significantly longer work duration of 60s compared to 45s and the much shorter pause between each set of only 30s against 2 min during conventional strength training. MAIORANA et al. (2000) demonstrated in a study with CHF patients that a circuit training programme interspersed with alternating bouts of aerobic and resistance exercise, separated by minimal rest periods, maintains HR and VO_2 within an effective training zone throughout the exercise session which led to an increase of aerobic capacity. The rate pressure product (RPP) was even lower after training, suggesting that myocardial oxygen demand decreased. It could be hypothesised that this may have resulted from increased peripheral vasodilation and thereby decreased the afterload following exercise [256]. The circuit training regime of MAIORANA et al. is in some parts very similar to this study where in the final training phase a 5 min. cycling exercise was introduced after every 3 stations of strength exercises. Not a single cardiac incidence occurred during the whole study in any of the training groups. Exemplary results of the comparison in blood pressure behaviour are presented in figure 45.

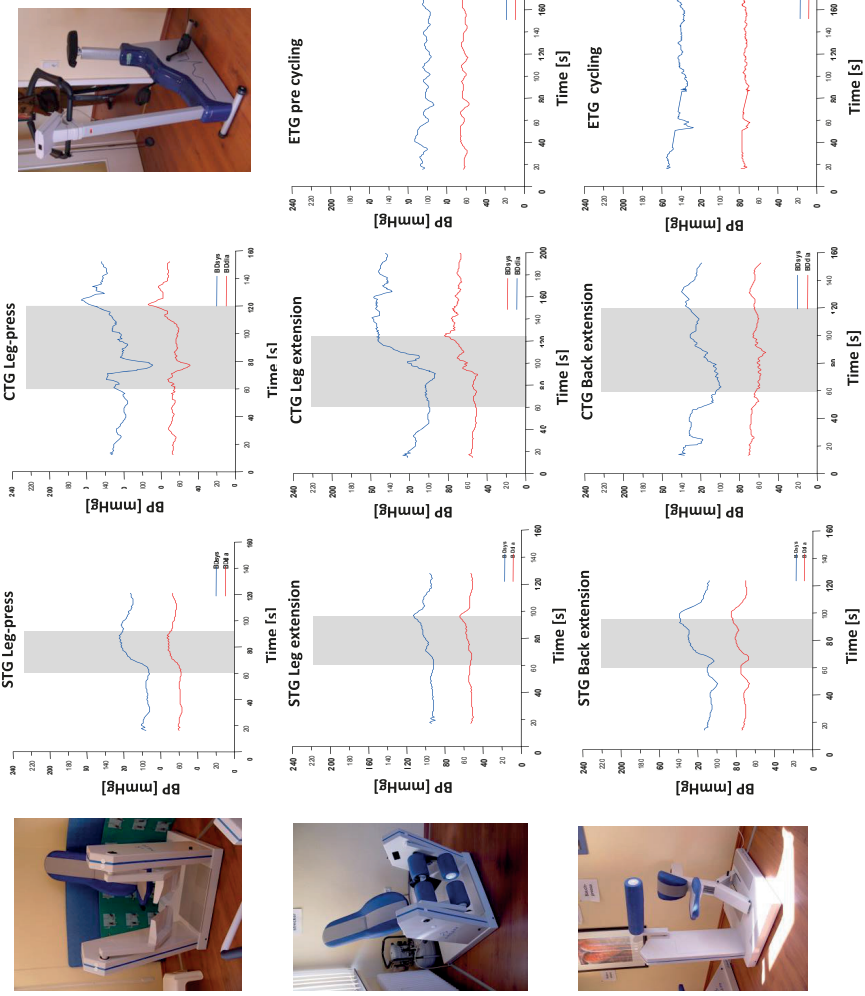

Figure 44: Exemplary blood pressure behaviour during high intensity strength training, circuit training and endurance training.

MCCARTNEY et al. (1998) also confirm decreased ischemia during strength training when compared with endurance exercise in a study performed with MI patients – probably due to improved coronary artery filling which results from an increased diastolic pressure in combination with decreased heart rate [258]. MAGNUSSEN et al. (1996) were the first to investigate the effects of a high-intensity strength training in CHF patients, but only using a knee extensor exercise. They reported significant improvements in muscle strength, capillarisation and oxidative capacity of the trained muscle group and without any adverse effects. However, cardiovascular performance was not tested [260].
The most relevant outcome of our study is the improvement in cardiac parameters– especially in EF and LVEDD. Dramatic increases like these are unknown from other publications and might be due to the relatively long intervention period of six months with a training frequency of 3 times per week over the majority of the 6 months and also the long duration of each session. However, the most important reason for these changes is probably the progressive and periodised approach in structuring the rehabilitative training. Every 4th exercise session a higher intensity and/or longer duration was tried in each individual patient although the intervention was carried out in a group setting. Thus, the patients were always working at their individual limit in each exercise in order to provoke anabolic responses. This way of systematically monitoring and adapting the training regime is common practice in competitive sports and can also be applied to high risk patients such as in the CHF and COPD populations – of course under supervision with adequate safety considerations and close monitoring. KLIJN P et al. (2013) had a similar approach with their study into *Nonlinear Exercise Training in Advanced COPD is Superior to Traditional Exercise Training: a Randomized Trial.* The authors found that non-linear periodised exercise training resulted in greater improvements in cycle endurance and health-related quality of life in patients with severe COPD than traditional training methods[261].

The findings of our CHF study suggest that the more severe the health situation of heart failure the greater the importance and the better the toleration of resistance training interventions are compared to endurance exercises. Regardless of the proportion of strength and endurance training, the actual systematic structure with appropriately high training stimuli to initiate an anabolic response and the progressive nature of a long term exercise programme following a periodization concept is of utmost importance.

COPD

Although it is generally accepted that in healthy subjects strength training interventions provoke very specific anaerobic adaptations, the biological responses in older people and in patients with chronic internal conditions is very different and can shift toward a broader adaptation process – including an increase in aerobic capacity as well as a probable muscle fibre shift from fast twitch to slow twitch fibres due to the slow movement in high intensity strength training and also the long work duration and short pauses in circuit training. This was the case in all three presented studies causing similar adaptations and measurable clinical effects in CHF and COPD patients.

Respiratory Function

In COPD study 1 the peak-flow data of the intervention group only shows a non-significant increase of 15L/min and 20L/min respectively. However, this was not found in the control group. The FEV_1 performance of the intervention group increased significantly by 5.3% which confirms the tendency of the peak flow values. In this context, it would be interesting to observe the long-term effects of such an intervention on respiratory function. An explanation for this must remain speculative. This type of resistance training potentially compensates the degeneration of the active and passive movement apparatus that is caused by disease-specific deconditioning processes in a manner that cannot be achieved by endurance training. Also, the associated compensation of muscular imbalances, which cause a restriction of the thorax, is possibly responsible for this effect. Beyond that, another effect is the strengthening of the auxiliary respiratory muscle [217]. Both aspects support an increase of respiratory function. The specific breathing technique used in strength training might have had additional positive effects similar to breathing exercises.

COPD study 2 also found a significant improvement in respiratory function in the FEV_1 in the intervention group (IMT) which confirms to some extent the effectiveness of inspiratory muscle training. However, it needs to be considered that these results were produced during only three weeks of hospitalisation while all other studies were conducted in an outpatient setting with much longer intervention duration. The respiratory strength also increased, as expected, significantly in the IMT group ($p<0.01$) as well as the respiratory strength and respiratory minute volume using the training device Respifit S ($p<0.01$).

Similar to the results presented in this study, LOTTERS et al. (2002) also found that IMT can significantly increase inspiratory muscle strength and inspiratory

muscle endurance [240]. Additionally the same author found in his review of the effects of IMT, a clinically significant decrease in dyspnoea sensation at rest and during exercise after IMT [240]. However, this could not be confirmed by this study. Only the comparison group showed a non-significant improvement in the dyspnoea item of the CRQ.

Endurance

The endurance performance in COPD study 1 measured by cycle ergometry showed a significant improvement of the intervention group (21.9W = 18.7%) in comparison to the control group (2.9W = 4%), which partly results from improved movement coordination (warm up and cool down on the stationary bike) [228]. However, such improvements cannot be explained purely by an improved coordination, since it is a quite simple technique. The better endurance performance was more likely caused by the increase in muscle mass, muscle power, as well as greater glycolytic capacity and changes in the enzymatic activity – possibly also muscle fibre shift toward more oxidative fibres (also see strength adaptations paragraph for more details).

This observation corresponds with the findings in healthy elderly subjects who showed that intensive resistance training has a positive effect on the oxidative metabolic capacity [218], which is contrary to adaptations in younger people to the same intervention. In this context, MALTAIS et al. demonstrated that COPD patients have a smaller amount of oxidative enzymes in muscle tissue compared to healthy subjects [229]. The lactate behaviour in this study confirms these findings, as a change in the lactate kinetics (right shift) was found in the intervention group. This means improved endurance performance through greater aerobic energy supply. COPD patients can develop their endurance performance positively on the basis of increased muscle strength. Thus, general physical performance could probably be improved quicker by muscle strength exercises than by endurance training in this population. For instance LEUPPI et al. only found an increase of 13.2W in maximal ergometry workload after a 4-month endurance training intervention in patients with moderate COPD [230].

The intervention group of COPD study 2, was able to improve their walking distance in the 6MWT from baseline to retest after 3 weeks of exercise therapy and IMT significantly by 11% while the comparison group also showed significant increases, but only by 4%. These results are similar to other studies such as found by REIS et al. (2013) in a study that investigated the long term effects of a mixed exercise intervention [170].

Strength

The results in all three presented studies regarding the improvement of strength performance and muscle functioning should not be underestimated as CHF and COPD patients display a marked decrease in muscular strength and endurance and much increased level of fatigability in ADLs. This can be explained by the general process of muscle wasting and/or sarcopenia, but also by a shift in muscle fibre typology with a decrease in the fatigue resistance slow twitch type I fibres [61,62] and a significant increase of type IIX fibres was found in COPD patients [61] which is comparable to the increase of type 2A fibres found in CHF patients [64]. GOSKER et al. were able to establish in a meta-analysis the correlation between loss in type I fibres and disease severity in COPD as well as determining reference values for fibre type proportions in healthy subjects in the typical age range for COPD GOLD stages 3 to 4 (60-70 years) for the vastus lateralis muscle and COPD patients. Individual studies consistently show a reduced proportion of type I fibres that was clearly confirmed by this meta-analysis by revealing a mean difference of 22% in the inter-study analysis and a mean difference of 18% in the intra-study analysis. Likewise, the proportion of fibre type IIX which was 13% higher in patients with COPD in both analyses [63].

This disease specific maladaptation assumingly was the baseline situation for the overall cohort of all three studies – CHF and COPD. Thus, a reversed muscle fibre shift probably took place by the various exercise interventions with the exception of the 3 week intervention in COPD study 2 as this is too short to produce these effects. The improvements in endurance performance thereby can be partially explained. These changes in muscle fibre composition cannot be confirmed as no muscle biopsies were conducted. However, a study by VOGIATZIS et al. (2011) proved these adaptations in muscle fibre remodelling in COPD stages II to IV as a response to a 10 week rehabilitation programme [262]. Duration and cohort characteristics were similar to the one in our study.

The intervention group in COPD study showed significant increases in strength performance in the 12 RM-Test in all test exercises ($p<0.01$) and also presented the same significant differences compared to the control group. The mean improvement in strength in all six test-exercises cumulated to 36.8% within the 12 week training period. These strength gains are slightly greater than in other strength training studies with COPD patients of similar intervention duration such as VELLOSO et al. (2013) [263] and BERNARD et al. (1999) who were only able to demonstrate improvements between 3% and 20% in a COPD cohort undergoing a combined strength and endurance exercise programme for 12 weeks [264].

In COPD study 2 the improvements in strength performance were also significant in both groups. The intervention group increased their strength in the Leg-press by 18% while the comparison group had an increase of 17%. The differences in the upper extremities tested by the Lat-pull exercise also showed significant improvements in both groups – in the intervention group by 25% and in the comparison group by 19% ($p<0.01$) which is significantly less than in COPD study 1. This can be explained by the short intervention duration of only 3 weeks compared to 12 weeks. These effects are nevertheless impressive and demonstrate the responsiveness of COPD patients to high intensity strength training.

Testosterone

The COPD study 1 also investigated free and total blood testosterone as a significant number of male COPD patients show disease specific low blood testosterone levels [55,56,57,58] as well as reduced levels of IGF-1 growth hormones [59,60]. The levels in blood testosterone (free and total) in our COPD study in all subjects also presented the typical testosterone deficit in COPD patients. The increase in free testosterone by 7.8% and total testosterone by 35.3%, however needs to be ignored as the frequency in blood sample taking would need to be at least daily to reflect any chronic biological changes of this parameter in a valid manner.

Both testosterone and growth hormones play a key role in anabolic skeletal muscle development. Growth hormone levels will deplete with age in the general population and this can cause age related changes in muscle. The extent of depletion in this population however is in excess of general age related reduction and it is considered to be an important factor of muscle dysfunction in COPD patients. Additionally steroid treatment contributes to these effects. Exactly the same catabolic changes can be observed in CHF patients. AGAPITOU et al. (2013) found the similar catabolic changes regarding IGF-1, growth hormone and testosterone in male CHF patients which was significantly associated with exercise intolerance, ventilatory inefficiency, and chronotropic incompetence in these patients [252]. They concluded that this is a significant contributing mechanism to the limited functional status of heart failure patients [260]. WEHR et al. (2011) confirmed that low levels of free testosterone in male heart failure patients are independently associated with increased CHF mortality [265].

Considering the overall physiological results of all three studies the applied training interventions – especially the progressive resistance training modalities

seem a sensible addition to the common therapy practice. Regarding the specific requirements for an effective CHF and COPD exercise therapy, strength training has a spectrum of advantages that cover – muscle hypertrophy, improved aerobic performance, not provoking dyspnoea as endurance exercises do and possibly a more specific effect on hormonal deficits. Resistance training generally causes a greater increase in testosterone than endurance training [231]. Another advantage might be that strength training is more likely to be better tolerated by these patients because of the intermittent nature of the exercise. Even patients with severe CHF and COPD are able to carry out an intensive training lasting up to 2 hours. This provokes a stronger disturbance in homeostasis, which in return initiates appropriate structure-developing anabolic biological responses.

MENTAL HEALTH ASPECTS OF EXERCISE THERAPY

COVENTRY et al. (2013) state that depression and anxiety are very common in patients with COPD and are associated with excess morbidity and mortality [271]. In their meta-analysis they found that *"… complex psychological and/or lifestyle interventions that include an exercise component significantly improve symptoms of depression and anxiety in people with COPD. Furthermore, multi-component exercise training effectively reduces symptoms of anxiety and depression in all people with COPD regardless of severity of depression or anxiety, highlighting the importance of promoting physical activity in this population…"* [266]. The consideration of mental health and quality of life aspects in any disease management programme for chronic internal diseases should therefore be an integral part as well as an important indicator for the success of an intervention. Hence, the parameter HRQL was used in all three of the above studies – only the tools differed and in the case of COPD study 1 even the depression profile of the cohort was analysed.

In COPD study 1 the St Georges Respiratory Questionnaire (SGRQ) was used and in COPD study 2 the Chronic Respiratory Questionnaire (CRQ) for measuring the effects of the exercise intervention on HRQL. Both questionnaires are widely used in the clinical and scientific community in the context of COPD. CRQ and SGRQ scores are reported on 7-point and 100-point scales respectively. The CRQ refers to domains or items of dyspnoea, fatigue, emotional function and mastery. Both questionnaires have proved valid and responsive [266].

A meta-analysis conducted by LACASSE et al. (2009) found that: "…*In most trials, health-related quality of life (HRQL) was measured by using either the CRQ or the*

SGRQ. Head-to-head comparisons of both questionnaires have been published …. In all studies, the analyses of reliability, validity and responsiveness did not clearly favour one instrument above the other. Rutten-van Mölken and colleagues … suggested that the choice between the CRQ and the SGRQ be based on other considerations such as the required sample size. Only one trial reported results from both the CRQ and the SGRQ …, without clear indication that one questionnaire is more sensitive to change than the other..." [267].

LACASSE et al. (2009) found in their review clinically and statistically significant improvements in important domains of quality of life, including dyspnoea, fatigue emotional function and mastery which can be confirmed in some areas by COPD study 2. LACASSE et al. also report another significant finding, when comparing the effects of pulmonary rehabilitation with the treatment effect of other important modalities of care for patients with COPD such as inhaled bronchodilators or oral theophylline and its new derivatives they found that rehabilitation resulted in greater improvements in important domains of health-related quality of life and functional exercise capacity [267].

In COPD study 1 the high intensity resistance training induced increases in physical exercise capacity that were also reflected in improved HRQL. However, a short-term decline of the HRQL in the intervention group was observed in the first 4 weeks. The explanation for this might be that the training intervention was a new stress factor at first, but then the patients slowly got accustomed to the training process. Thus, a significant increase in the HRQL was observed in this group from test 1 to 4, whereas the control group showed a trend of declining HRQL over the same period of time. In this context not only the physiological improvements may lead to an improved HRQL, but also the social aspect of exercise therapy in a group setting as well as psychological effects of sharing the stress of a severe chronic like this with others. CHF and COPD patients are generally at risk of social isolation and therefore depression. This has confirmed the results of the BDI questionnaire which presented the cohort of 28 COPD patients with a significantly higher score of 11.29 compared to a healthy population that is referenced with a score of 6.45 [227]. COPD patients are therefore closer to psychosomatic pain patients who usually achieve a mean value of 11.4 in depression symptoms. However, the population of depression patients are referenced with a much higher score of 23.7 [227].

The second COPD study not only showed significant increases in all components of exercise ($p \leq 0.01$) ranging from 11% improved endurance to 25% strength increases, but also clinically relevant results concerning the HRQL. The

intervention group (IMT) scored significantly higher in the items *mastery* and *emotional function* compared to the comparison group. FOY et al. (2001) demonstrated in their study that long-term exercise therapy has little added benefit for women over a short term exercise therapy. However, men derived significant benefits from extended training [268].

The CHF study was not able to prove any significant changes in HRQL using the Minnesota living with Heart failure Questionnaire (MHFQ) in any of the groups, which stands in contrast to the dramatic physiological improvements and the findings in both COPD studies. No comparable study was found in the literature that produced similar results in HRQL. An explanation of the lack of reported improvement of HRQL remains speculative. One possible reason might be the long duration of the intervention and overall participation duration in this study of each individual. This was up to 8 months and the increase in cardiac and exercise capacity and functioning slowly developed over that duration and therefore did not appear drastic enough to the patients and thereby led to this result. Another explanation is the sensitivity of the questionnaire tool itself – although there is no indication for this interpretation in the literature.

THEORY AND PRACTICE

DISCREPANCIES BETWEEN EVIDENCE AND PRACTICAL APPLICATION

The role of exercise as part of a multidisciplinary approach to the management of CHF and COPD is essential - especially with regard to cardiac and pulmonary rehabilitation. Yet it is unacceptably underutilised as BUTTS et al. (2013) state in a recent publication: *"… Although medical management of COPD is generally well understood and implemented by most primary care physicians, multidisciplinary approaches that include non-pharmacologic modalities are not often used. Exercise training can alleviate dyspnoea and improve exercise tolerance and health-related quality of life in patients with mild-to-severe COPD. Pulmonary rehabilitation, which includes exercise training, nutritional and psychological counselling, and patient education, is an important component of COPD treatment and management programmes, and is currently underutilised in the United States..."* [269].

This statement is confirmed by the findings of all three studies presented in this publication. However, the extreme improvements found in the CHF study with longest intervention duration of 6 months, regarding cardiac parameters, proves

that some effects such as a reduction in size of the enlarged heart of CHF patients, can neither be produced by conventional drug therapy nor dietary interventions.

Thus, it is difficult to accept that this cost effective and multi-potent therapy is not widely used in both conditions. Part of the problem was identified by GLAAB et al. (2006) in their study assessing the recommendations of office-based pulmonary specialists in Germany regarding the outpatient management in relation to current guideline recommendations for COPD [270]. A nationwide prospective cross-sectional study was therefore conducted using a COPD questionnaire survey. A total of 590 pulmonary specialists participated in this survey. The findings suggested that most pulmonary specialists adhere to the current COPD guideline recommendations. However, necessary changes in the health care system were recommended including more effective ways of knowledge transfer to clinical – especially concerning the evidence of exercise interventions as the authors found that referral for pulmonary rehabilitation was uncommon, regardless of the severity of COPD [270]. This essentially prevents COPD patients from accessing a therapy with one of the highest evidence levels in the management of pulmonary disease. The situation in cardiac rehabilitation is generally better, but not necessarily for CHF patients as many physicians still recommend rest and/or low level exercise to their patients. Similar results were found by BROOKS et al. (1999) who state that in Canada, a national survey conducted in 1999 indicated that less than 2% of the population with COPD per annum has access to a rehabilitation programme [271]. Hence, it can be concluded that the lack of accessibility to specific exercise programmes for CHF and COPD patients is a global problem and needs to be addressed by professional associations and politicians – especially when considering the long term health economic implications.

SAFETY ASPECTS

A reason for not applying effective progressive, non-linear exercise interventions are often unreasonable worries about safety as well as insufficient knowledge of exercise physiology and conditioning methods. All major studies referenced in this work have confirmed the safety and benefit of structured exercise interventions in the treatment of CHF and COPD. A prime example for proving the safety of structured exercise programmes in high risk patients is the presented CHF study which compared different exercise regimes – of which some were even using high intensity methods over a period of 6 months.

During almost 10.000 hours of exercise training with patients of the NYHA classes II and III in this study not a single incident occurred. The only cardiac incident that occurred was during maximal exercise testing outside the normal rehabilitation setting, when a defibrillator was set off by arrhythmias while an incremental cycle ergometry had been conducted.

Part of the safety net was a multi-disciplinary approach which included a weekly examination of each patient before exercising by a cardiac nurse and the supervision of the training by a qualified exercise specialist. High intensities were used in both resistance training methods and proved to be safe. In the high intensity strength training group even maximal workloads were accomplished without any problems. This also included overhead workouts such as shoulder press and Lat-pull. In this context blood pressure behaviour was measured during different exercise interventions using the FinaPress (see fig 45). The aim was to investigate whether there is a difference between endurance training and forms of resistance training under special consideration of dangerous blood pressure peaks. There was no significant difference between the various interventions and at all times the blood pressure was within acceptable limits [systolic below 220 mmHg].

HEALTH ECONOMIC IMPLICATIONS

Economic studies suggest that cardiac and pulmonary rehabilitation can be justified on financial grounds alone. In a publication of LEVIN et al. (1991) a Swedish study was presented which found that after attending a comprehensive exercise programme 51% of the rehabilitated patients were at work five years after their MI compared with 27% of those not rehabilitated. This appeared to be due to lower levels of anxiety and depression and fewer acute events. The authors concluded that this represented savings of $10.000 per patient [272].

The following cost calculations based on the presented CHF study prove that a systematic exercise therapy in an outpatient setting such as in "Herzsportgruppen" in Germany or *Exercise Referral Schemes* in the UK are cost effective and that patients are willing to pay a contribution towards the overall costs. If only 30% of all CHF patients would participate in these schemes, the direct annual cost savings would be approx. £ 100 million (UK), and 216 million Euros (Germany). The overall annual savings (including any additional savings such as lost work days etc.) might be as high as £1 billion in the UK and almost 2 billion Euros in Germany if the majority of CHF patients participated in structured exercise programmes. The central parameter in this context is the hospitalisation

rate which demonstrated a significant reduction between the training groups with 15% and the control group with 36% over the same period of time.

The above figures were calculated as approximate values based on simplified assumptions and are not professional health economic calculations:

Hospitalisation Costs
An average of 10 days per hospitalisation
160-200 Euros a day (small country hospital)
250 Euros a day (major hospital)
= approx. 230 Euros
230 Euros x 10 days = 2300 Euros per patient and hospitalisation

Rehabilitation Costs
Training/Exercise intervention per month 107 Euros
After 1 to 3 years 40% of all patients who were included in the study are still exercising twice a week in a referral programme setting and finance their own training with 65 Euros each month – this covers room rent, specialised staff and equipment. The health insurance is covering 6.50 Euros per exercise session which equates to 42 Euros/month plus the patients' contribution of 65 Euros = 107 Euros.

Cost Calculation
Control Group
9 hospitalisations = 36% of patients in the control group.
All Intervention Groups
10 hospitalisations = 15.4% of patients in the intervention group.

- 1 hospitalisation = average of 10 days
- One day in a German hospital costs an average of 230 Euros

The following figures in the cost calculation refer to all the patients who completed the study (also see "CHF study Methodology"), excluding the subjects who dropped out for personal reasons.
Control group
20.700 Euros = 828 Euros per patient in 6 months = 138 Euros per month
Intervention group
23.000 Euros = 330 Euros per patient in 6 months = 55 Euros per month

Savings

Intervention group

47 Euros (6.50 Euros per session) paid by the health insurance per month. In addition another 65 Euros paid by the patient as a substitute for rent and equipment in this specific setting of the study. Plus an average of 55 Euros hospitalisation per month.

47 + 55 = 102 Euros a month

Without exercise intervention 138 Euros.

Savings = 36 Euros per patient and month

If **30% of all CHF patients** in Germany (approx. 1.450.000 Germany/ 1.000.000 UK) would undergo a specific exercise intervention for CHF the overall savings (excluding any savings in medication) would be:

36 Euros × approx. 500.000 = **18.000.000 Euros savings a month in Germany**

18 million x 12 months = **216.000.000 Euros savings a year in Germany**

This exemplary cost effectiveness calculation could be applied to all long-term exercise related studies to demonstrate the potential and necessity of exercise therapy in the disease management of most health conditions. This paradox situation of evidence for the therapeutic effectiveness of an intervention and the cost-effectiveness of the same with the reality of not being exploited to the maximum by health care systems could not be better explained than by one of the world leading experts in sports medicine – Professor Wildor Hollmann who asked the auditorium during a presentation:

"If there was a drug that would combine the following effects:

Reducing the myocardial oxygen consumption, inhibiting the development of arteriosclerosis, improving the blood viscosity combined with anti-thrombosis effects, prevention of obesity, supporting an optimal physical and mental development, preventing ageing associated physical and mental decline - with what enthusiasm would such a drug be celebrated worldwide?

But this medication already exists: it is called an adequate, individually fitted physical training from childhood up to the oldest age. Unfortunately we have to live with the physical law of inertia [laziness] which is preventing its use."

(Hollmann, 1995).

Conclusions

In the case of the heart failure study the patients of all exercise groups could be reclassified according to the NYHA-system by one stage. It can be also stated that at no time cardiac problems occurred. Furthermore, it can be pointed out that an outpatient training therapy finds a high acceptance in these patients and is practicable at the same time. The results and experience demonstrate the safe feasibility of different outpatient exercise interventions and suggest specific positive adaptations in patients with chronic heart failure which also lead to a lower hospitalisation rate. There are clear hints that the therapy spectrum could be supplemented significantly in the near future by specific training interventions. The financial implications for any health care system are also highly relevant.

Regarding the two smaller COPD studies it can be concluded that high intensity strength training is safe and well tolerated by COPD patients with or without oxygen therapy. It compensates for COPD specific maladaptation and improves exercise capacity in all aspects that thereby translate in improved health related quality of life. Inspiratory muscle training in addition to conventional exercise therapy improves FEV_1 as well as inspiratory muscle strength and endurance, functional exercise capacity (6MWT) and HRQL which could lead to improved activities of daily living. However, further research is needed to explore the impact that different training protocols may have on clinical outcomes as well as different intervention durations during common hospitalisation periods, i.e. 3 weeks vs. 4 vs. 5 weeks.

Five main conclusions can be derived from the three studies in to the effects of different exercise interventions in CHF and COPD:

1. Exercise interventions are safe and cost-effective in high risk populations.
2. In heart failure specific exercise interventions can reverse the effects of CHF regarding cardiac function and the hypertrophic myocardium to a clinically relevant extend.
3. The applied progressive exercise regimes demonstrate the need for more structured non-linear exercise programmes in the rehabilitation of CHF and COPD.
4. A novel exercise therapy concept of joint exercises classes for CHF and COPD patients is needed in order to translate evidence based exercise regimes in to the standard disease management of CHF and COPD and thereby filling the significant and unacceptable health care gap for these patients.

5. In this context there is also a requirement for CHF/COPD specialised and highly qualified exercise instructors (UK possibly level 5 (provided by WRIGHT Foundation and the like), Germany specialised vocational training – exclusively for CHF and COPD (provided by DVGS and the like).

7 SUMMARY

The increase of prevalent conditions such as obesity, diabetes mellitus, respiratory and cardiac diseases lead to exploding costs in health care systems. Some of the most costly conditions are chronic heart failure (CHF) which has a high prevalence especially in the older population and may affect as much as 10% of this cohort (U.S.A) [1], and chronic obstructive pulmonary disease (COPD) has shown one of the most dramatic increases in mortality in the developed world over the past 40 years. Both are therefore leading causes of morbidity and mortality worldwide and should be considered as a major economic and social burden that is both substantial and increasing [3].

In both conditions, exercise therapy should play an integral part in maintaining the patient's maximal level of independence and functioning, as well as slowing or possibly even stopping the progression of the condition. In this context the main objectives for these doctoral theses are:

a. Proving the safety of different exercise modalities.
b. Identifying the most effective exercise interventions in regards to clinical parameters.
c. Proving the feasibility of outpatient rehabilitation programmes for these high risk populations.

This work, therefore, combines three studies looking into the effects of non-pharmaceutical interventions – predominantly different exercise regimes in the two major conditions in the mortality statistics of chronic, or also known, as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) both are classed as so called "end-stage conditions" with a very poor prognosis.

CHF Study

The aim of the CHF study was to examine the physiological effects of various exercise training methods on CHF patients. 125 patients were randomised and divided into an endurance group (ETG, n=25), a high intensity strength training group (STG, n=25), a circuit training group (CTG, n=25) and a dietary comparison group or non-training group (CPG, n=25) as well as a control group (CG, n=25). The interventions took place over a period of six months with three testing points. 78 patients of the exercise groups and the CPG completed the study and 18 of the CG.

The results showed that EF increased significantly in all training groups at all test points (ETG: pre 31±6% post 46±8%; CTG: pre 29%±7% post 45%±11%; STG: pre

30%±7% post 45%±7%), but no significant change in the CPG was found. All exercise groups showed a significant improvement in the NYHA-classification by one class. The NT-pro-BNP showed a significant decrease from 1495±1555 pg/mL to 934±702 in the ETG (post vs. pre, $p<0.01$) and the CPG of 1557±907 to 1105 pg/mL (interim vs. pre, $p<0.05$). Finally the peak VO_2 showed no significant changes in the CPG, but again significant changes in all the training groups. No training-related adverse effects were reported in any intervention group. The hospitalisation data showed a significant decrease in the hospitalisation rate between the training groups and CPG ($p<0.01$) within 30. The hospitalisation rate of CPG was 33% for that duration compared to 15% in the exercise intervention groups and even higher in the control group with 36% over the same period of time. This data refers to a total n= 96 (including 78 intervention and comparison group patients and 18 control group patients). The mortality rate also presented significant differences between the groups. All the patients in the three training groups had a mortality rate of 3.1% whereas the control group showed a 28% mortality within 30 weeks. The mortality rate of the training groups was therefore significantly lower ($p<0.001$). The CPG showed a slightly higher mortality rate than the exercising groups, but still significantly lower than the control group. This data was collected additionally to the aforementioned other measurements and therefore include the control group (n=25). The total number of patients for this parameter was n= 105.

The supervised outpatient exercise training was safe and beneficial in CHF patients with NYHA stage II and III. All exercise interventions have a positive effect on cardiovascular and exercise specific parameters, but there is no significant difference between the various exercise interventions. Percentage wise the high intensity strength training group produced the greatest effects. This should be further examined.

COPD Study 1

In the COPD rehabilitation practice mainly endurance training is used as the preferred exercise intervention for these patients. Because of the specific symptoms (e.g., muscle atrophy, dyspnoea, low testosterone levels) and the de-conditioning, resistance training might meet the demands of a COPD-exercise-therapy rather than endurance training. The aim of this research project was to evaluate the effects of strength training on various COPD-relevant parameters.

Twenty-eight patients with moderate to severe COPD (12 male, 16 female) were randomised and divided into an intervention and a control group (CG). The patients in the intervention group (STG) underwent a high intensity strength

training for 12 weeks, initially twice, then 3 times a week for 60 to 120 min. Results referring to the FEV_1 performance showed a significant increase ($p= .01$) of 5.3% in the STG, whereas in the daily peak-flow measurement presented no significant change in both groups, a trend towards an improvement of this parameter was found in the STG by 20 L/min. The performance in the cycle ergometry showed a significant improvement ($p< .001$) of the STG by 18.7% (21.9 W). The results of the St. George's Respiratory Questionnaire also showed a significant improvement ($p< .05$) of the health-related quality of life (HRQL) in the STG. A change of the HRQL in the CG was not found. Also, the overall cohort was analysed for symptoms of depression and presented significantly higher symptoms than a healthy population. This cohort was just below the same score as psychosomatic pain patients.

It can be concluded that a 12 week high-intensity strength training programme is suitable to improve pulmonary function and performance measurements of patients with moderate to severe COPD. These changes lead to an improved health related quality of life. Therefore, high intensity resistance training is suitable for a more specific COPD exercise therapy and offers new treatment perspectives – especially in severe cases as the intermittent structure of strength training suits the disease specific symptoms of COPD patients more as they are usually struggling when undergoing longer endurance exercises because of increased dyspnoea and muscular fatigue.

COPD study 2

Inspiratory muscle training (IMT) is becoming more popular in pulmonary rehabilitation, but is usually used in combination with other interventions [232]. However, companies do advertise IMT devices not only as an add-on therapy, but sometimes as a possible alternative to whole body exercise therapy. There is yet no scientific proof that IMT can produce similar results to conventional rehabilitative exercise interventions.

Thus, the second COPD study investigated the effects of a 3 week IMT plus conventional exercise versus a conventional exercise therapy in COPD patients in a hospital setting. 44 COPD patients GOLD II to IV were stratified and allocated to the intervention group (IMTG, n=22) and comparison group (CPG, n=22) in order to have a comparable sample profile in each group. This study only found a significant improvement in respiratory function in the FEV_1 in the intervention group with IMT which confirms, to some extent, the effectiveness of IMT. However, it needs to be emphasised that these results were produced during only three weeks of hospitalisation while all other studies were conducted in an

outpatient setting with much longer intervention duration. The respiratory strength also increased as expected significantly in the IMTG ($p<0.01$). These results were also confirmed by the respiratory strength and respiratory minute volume measurements using the training device Respifit S ($p<0.01$). The IMTG showed significant increases in two HRQL items in the CRQ – mastery and emotional function, while the comparison group showed a non-significant improvement in the dyspnoea item of the CRQ.

Regardless of the effects of IMT, this study confirms the effectiveness of a three week hospitalised rehabilitation programme. This cohort of COPD patients showed significant increases in all components of exercise ($p\leq0.01$) ranging from 11% improved endurance to 25% strength increases. This leads to the conclusion that IMT in addition to conventional exercise therapy improves FEV_1 as well as inspiratory muscle strength and endurance, functional exercise capacity (6MWT) and health related quality of life.

In conclusion it can be said that the results and experience of the CHF study demonstrate the safe feasibility of different outpatient exercise interventions and suggest specific positive adaptations in patients with heart failure which also lead to a lower hospitalisation rate. There are clear hints that the therapy spectrum could be supplemented significantly in the near future by specific training interventions. The financial implications for any health care system are also highly relevant.

Regarding the two smaller COPD studies it can be concluded that high intensity strength training is safe and well tolerated by COPD patients with or without oxygen therapy. It compensates for COPD specific maladaptation and improves exercise capacity in all aspects that thereby translated in improved health related quality of life. Inspiratory muscle training in addition to conventional exercise therapy improves FEV_1 as well as inspiratory muscle strength and endurance, functional exercise capacity (6MWT) and HRQL which could lead to improved activities of daily living.

Five main conclusions can be derived from the three studies in to the effects of different exercise interventions in CHF and COPD:

1. Exercise interventions are safe and cost-effective in high risk populations.
2. In heart failure specific exercise interventions can reverse the effects of CHF regarding cardiac function and the hypertrophic myocardium to a clinically relevant extent.
3. The applied progressive exercise regimes demonstrate the need for more structured non-linear exercise programmes in the rehabilitation of CHF and COPD.
4. A novel exercise therapy concept of joint exercises classes for CHF and COPD patients is needed in order to translate evidence based exercise regimes in to the standard disease management of CHF and COPD and thereby filling the significant and unacceptable health care gap for these patients.
5. In this context there is also a requirement for CHF/COPD specialised and highly qualified exercise instructors (UK possibly level 5 (provided by WRIGHT Foundation and the like), Germany specialised vocational training – exclusively for CHF and COPD (provided by DVGS and the like).

ZUSAMMENFASSUNG

Die Zunahme von prävalenten Erkrankungen wie Adipositas, Diabetes Mellitus sowie Lungen- und Herzkreislauferkrankungen führen zu explodierenden Kosten in den Gesundheitssystemen. Einige der kostenintensivsten Erkrankungen sind die *Chronische Herzinsuffizienz* (CHF) mit einer hohen Prävalenz, insbesondere in der älteren Population mit bis zu 10% (U.S.A.) – wobei Männer häufiger betroffen sind als Frauen [1], und die *Chronisch Obstruktive Lungenerkrankungen* oder auch in der Fachwelt *Chronic Obstructive Pulmonary Disease* (COPD) genannt. Letztere verzeichnete in den letzten 40 Jahren eine dramatisch Zunahme von bis zu 156% in der entwickelten Welt. COPD ist somit eine der führenden Ursachen für Morbidität und Mortalität und wird heutzutage als eine der größten ökonomischen und sozialen Herausforderungen angesehen[3].

Bei beiden Erkrankungen sollte die Sport- bzw. Bewegungstherapie eine zentrale Rolle spielen, um eine möglichst hohe Selbständigkeit und Mobilität bzw. *Functioning* zu erhalten – ebenso wie den fortschreitenden Krankheitsverlauf zu verlangsamen oder möglicherweise sogar aufzuhalten. In diesem Zusammenhang waren die Hauptziele dieser Dissertation:

a. Die Sicherheit verschiedener Trainingsmodalitäten nachzuweisen.
b. Die effektivste Trainingsmethode zu identifizieren bzgl. klinischer Parameter.
c. Modelle für die praktische Durchführbarkeit von ambulanten Rehabilitationsprogrammen mit Hochrisikopatienten aufzuzeigen.

Diese Arbeit vereinigt demnach drei Studien, welche sich mit den Effekten nicht-pharmakologischer Interventionen beschäftigen. Hauptsächlich wurden dabei verschiedene sporttherapeutische Programme in der Rehabilitation der chronischen Herzinsuffizienz und COPD untersucht. Als sogenannte „End-stage" Erkrankungen mit extrem schlechter Prognose, bilden sie in der Mortalitätsstatistik zwei der Haupterkrankungen.

CHF Studie

Das Ziel der CHF Studie war es die physiologischen Effekte verschiedener Trainingsmethoden bei Herzinsuffizienz-Patienten zu untersuchen. 125 Patienten wurden hierfür randomisiert und auf eine Ausdauertrainingsgruppe (ETG, n=25), eine High-Intensity Krafttrainingsgruppe (STG, n=25), eine Zirkeltrainingsgruppe (CTG, n=25) sowie eine diätische Vergleichsgruppe (CPG, n=25) und eine Kontrollgruppe (CG, n=25) aufgeteilt. Die Interventionsdauer betrug 6 Monate,

mit 3 Testzeitpunkten, wodurch jeder Proband insgesamt 8 Monate in die Studie involviert war. 78 Patienten aus den sporttherapeutischen Gruppen und der NTG beendet die Studie, ebenso 18 Patienten aus der CG.

Die Ergebnisse zeigten, dass die EF in allen Trainingsgruppen signifikant zu allen Testzeitpunkten zugenommen hatte (ETG: prä 31±6% post 46±8%; CTG: prä 29%±7% post 45%±11%; STG: prä 30%±7% post 45%±7%), es aber keine signifikanten Veränderungen in der CPG gab. Alle Trainingsgruppen zeigten ebenfalls eine signifkante Verbesserung in der NYHA-Klassifizierung um eine Stufe. Die NT-pro-BNP Werte waren ebenfalls signifikant reduziert (Verbesserung) von 1495±1555 pg/mL auf 934±702 in der ETG (post vs. prä, $p<0.01$) und in der CPG von 1557±907 auf 1105 pg/mL (interim vs. prä, $p<0.05$). Schließlich zeigte die $VO_{2\ peak}$ in der CPG keine signifikanten Änderungen, hingegen aber in allen Trainingsgruppen. Adverse Effekte wurden in keiner der Interventionsgruppen beobachtet. Bezüglich der Hospitalistion konnte eine signifikante Abnahme der Hospitalisationsrate zwischen den Trainingsgruppen und der CPG ($p<0.01$) innerhalb der 30 Wochen gezeigt werden. Dabei betrug die Hospitalisationsrate über demselben Zeitraum in der CPG 33%, verglichen mit 15% der sporttherapeutischen Interventionsgruppen (ETG, STG, CTG) und sogar 36% der CG. Diese Daten beziehen sich auf ein Gesamt-n von 96 Patienten (78 Patienten aus den Interventionsgruppen und der Vergleichsgruppe plus 18 Patienten aus der Kontrollgruppe). Die Mortalitätsrate präsentierte ebenfalls signifikante Unterschiede zwischen den Gruppen. Alle Patienten aus den Trainingsgruppen hatten eine Mortalität von 3.1%, wobei die CG innerhalb der 30 Wochen eine Mortalität von 28% aufwies. Die Mortalitätsrate in den Interventionsgruppen war damit höchst signifikant niedriger ($p<0.001$). Die CPG zeigte eine leicht höhere Sterblichkeit als die Trainingsgruppen, aber immer noch signifikant niedriger als die CG. Letztere Daten wurden zusätzlich zu den bereits beschriebenen Daten/Parametern gesammelt und beziehen sich auf die gesamte Kohorte. Daher ergab sich für die Mortalität ein Gesamt-n von 105 Patienten.

Die angeleitete Sporttherapie erwies als sicher und effektiv für die CHF-Patienten mit einer NYHA-Klasse von II und III. Alle Trainingsinterventionen hatten positive Effekte auf kardiovaskuläre Parameter sowie Leistungsparameter. Allerdings konnten insgesamt keine signifikanten Unterschiede zwischen den untersuchten Trainingsmethoden festgestellt werden – obgleich sie in einzelnen Parametern stark differierten. Prozentual zeigte die High-Intensity Krafttrainingsgruppe die stärksten Effekte. Dies sollte in Zukunft weiter untersucht werden.

COPD Studie 1

In der COPD Rehabilitationspraxis werden hauptsächlich Ausdauerprogramme als bevorzugte sporttherapeutische Intervention eingesetzt. Aufgrund der spezifischen Symptomatik (z.B. Muskelatrophie, Dyspnoe, niedrige Testosteron- und Wachstumshormon-Level) und der Dekonditionierung dieser Patienten, könnte Krafttraining u.U. die Anforderungen an eine COPD-spezifische Sporttherapie besser erfüllen als ein Ausdauertraining. Daher war das Ziel der COPD Studie 1 die Effekte eines High-Intensity Krafttrainings auf verschiedene COPD-relevanten Parameter zu untersuchen.

Dafür wurden 28 Patienten mit moderater bis sehr schwerer COPD (GOLD I bis IV) – davon 12 männlich und 16 weiblich – randomisiert und einer Interventionsgruppe (STG) sowie einer Kontrollgruppe (CG) zugeordnet. Die Patienten in der IG unterzogen sich einem hochintensiven Krafttraining für 12 Wochen, anfangs zweimal wöchentlich, dann dreimal für je 60 (anfangs) bis 120 (Endphase) Minuten. Die Ergebnisse bzgl. der FEV_1 zeigen einen hoch signifikanten Anstieg ($p<0.01$) um 5.3% in der STG, wobei die Peak-Flow-Werte keine signifikanten Unterschiede aufwiesen. Lediglich eine tendenzielle Verbesserung der STG um 20L/min konnte festgestellt werden. Die Leistung in der Fahrradergometrie stieg in der STG höchst signifikant um 18.7% an, was 21.9W entsprach ($p<0.001$). Die Ergebnisse des St. George's Respiratory Questionnaire wiesen ebenfalls signifikante Steigerungen der STG von prä zu post bzgl. der Gesundheitsbezogenen Lebensqualität (HRQL) auf. Keine Änderung wurde diesbezüglich in der CG festgestellt. Ebenso wurde in der Gesamtkohorte nach Depressionssymptomatik untersucht und festgestellt, dass diese Population einen signifikant höheren Summenscore für Depression zeigte als eine gesunde Vergleichspopulation und damit nur leicht unter den Referenzwerten für psychosomatisch kranke Schmerzpatienten lag.

Schließlich konnte somit gezeigt werden, dass ein 12 wöchiges High-Intensity Krafttrainingsprogramm geeignet ist, um Lungenfunktions- und Leistungsparameter bei Patienten mit moderater bis sehr schwerer COPD zu verbessern. Diese Verbesserungen übersetzten sich in eine gesteigerte gesundheitsbezogene Lebensqualität. Daher ist ein hochintensives Krafttraining für die spezifische sporttherapeutische Behandlung von COPD geeignet und offeriert neue Behandlungsperspektiven. Dies gilt insbesondere für schwere Fälle, wie bei GOLD III und IV Patienten, da die intermittierende Belastungsstruktur des Krafttrainings den krankheitsspezifischen Symptomen der COPD besser entgegen

kommt als Ausdauertraining, bei welchem diese Patienten normalerweise Probleme durch verstärkte Dyspnoe und frühzeitige Muskelermüdung haben.

COPD Studie 2

Inspiratorisches Muskeltraining (IMT) nimmt in der pulmologischen Rehabilitation immer mehr an Popularität zu und wird normalerweise in Kombination mit anderen sporttherapeutischen Interventionen angewandt [232]. Allerdings zielen manche Hersteller von IMT Geräten nicht nur auf eine Ergänzung zur konventionellen Therapie, sondern werben ebenfalls damit, dass sie eine mögliche Alternative zur Sporttherapie darstellen können. Dafür gibt es aber bisher keine wissenschaftlichen Hinweise.

Diese zweite COPD Studie hat die Effekte eines 3 wöchigen IMT in Kombination mit einer konventionellen Sporttherapie versus alleiniger Sporttherapie in einem Rehaklinik-Setting untersucht. Hierfür wurden 44 COPD-Patienten (GOLD II bis IV) nach Schweregrad, Symptomatik und Geschlecht stratifiziert und einer Interventionsgruppe (IMTG, n=22) sowie einer Vergleichsgruppe (CPG, n=22) zugeordnet. Die Ergebnisse stellten signifikante Unterschiede zwischen beiden Gruppen bzgl. der FEV_1 fest, was die Effektivität dieses zusätzlichen Trainings zeigt.

Dabei sollte allerdings betont werden, dass diese signifikanten Ergebnisse in nur 3 Wochen erzielt wurden, was in dieser Form in der Literatur bisher nicht beschrieben wurde bzw. die meisten anderen Studien entweder im ambulanten Setting bzw. über wesentlich längere Interventions-Zeiträume stattfanden. Die respiratorische Kraft stieg in der IMTG wie erwartet signifikant an ($p<0.01$). Dieses Ergebnis wurde durch das signifikant gesteigerte Atemminutenvolumen mit dem, zum Training eingesetzten, Respifit S ($p<0.01$) ergänzt. Die IMTG wies ebenfalls signifikante Verbesserungen in zwei der Items des CRQ zur gesundheitsbezogenen Lebensqualität auf – *Mastery* und *Emotional Function*. Die Vergleichsgruppe zeigte eine tendenzielle, aber nicht signifikante Verbesserung im *Dyspnoea*-Item.

Unabhängig von den Effekten des IMT, konnte diese Studie die Effektivität eines 3 wöchigen hospitalisierten Rehabilitationsprogrammes nachweisen. Die Kohorte der COPD Patienten zeigte hoch signifikante Steigerungen in allen konditionellen Komponenten auf ($p\leq0.01$), welche von 11% Ausdauerleistungssteigerung bis hin zu 25% Kraftsteigerung rangierten. Zusammenfassend kann gesagt werden, dass ein IMT zusätzlich zu einer konventionellen Sporttherapie sinnvoll ist und die FEV_1 sowie die inspiratorische Muskelkraft und-Ausdauer signifikant steigert. Dies gilt

ebenfalls für die funktionelle Leistung im 6MWT sowie die gesundheitsbezogene Lebensqualität.

Schlussfolgernd kann aus den vorliegenden Ergebnissen und Erfahrungen der CHF Studie gesagt werden, dass eine ambulante Sporttherapie praktikabel und sicher ist und zu spezifischen positiven Adaptationen bei Herzinsuffizienzpatienten führt, welche eine deutliche reduzierte Hospitalisationsrate zur Folge haben. Es gibt deutliche Hinweise dafür, dass das Therapiespektrum mit spezifischen Trainingsintervention ergänzt und damit deutlich verbessert werden könnte. Die Gesundheitsökonomischen Implikationen dabei sind ebenfalls höchst relevant.

Bezüglich der beiden kleineren COPD Studien kann konkludiert werden, dass ein High-Intensity Krafttraining sicher ist und von den Patienten gut toleriert wird – mit und ohne Sauerstofftherapie. Es kompensiert COPD spezifische Maladaptationen und verbessert die körperliche Leistungsfähigkeit soie Belastbarkeit und bewirkt dadurch eine verbesserte gesundheitsbezogene Lebensqualität. Ein inspiratorisches Muskeltraining in Kombination mit Sporttherapie verbessert ebenfalls Lungenfunktionsparameter und die funktionelle Leistungsfähigkeit sowie einige Aspekte der Lebensqualität, was in der Summe wahrscheinlich zu gesteigerten Aktivitäten des täglichen Lebens führt.

Fünf Hauptschlussfolgerungen können von den Ergebnissen und Erfahrungen der drei vorliegenden Studien zu CHF und COPD gezogen werden:

1. Sporttherapeutische Interventionen mit Hochrisikopatienten sind sicher und kosteneffektiv.
2. In der Behandlung von CHF können spezifische sporttherapeutische Interventionen einige der Effekte der Herzinsuffizienz, wie kardiale Funktion und das krankhaft vergrößerte LVEDD des Herzens in einem klinisch relevanten Maße umkehren.
3. Die angewandten progressiven Trainingsmethoden demonstrieren die Notwendigkeit für besser strukturierte, nicht-lineare bzw. periodisierte Bewegungsprogramme in der Rehabilitation von CHF und COPD.
4. Ein neues Sporttherapiekonzept mit gemeinsamen Gruppentherapien von Herzinsuffizienzpatienten und COPD-Patienten sind notwendig, um evidenzbasierte Trainingsmethoden in den Therapiealltag zu übertragen, damit zum Standard im Disease Management von CHF und COPD werden und dadurch eine immer noch deutliche und nicht akzeptierbare Versorgungslücke für diese Patienten im Gesundheitssystem schließt.

5. In diesem Zusammenhang besteht die Notwendigkeit für hochqualifizierte und spezialisierte Sporttherapeuten in Deutschland – exklusiv für CHF/COPD-Therapie, zusätzlich ausgebildet durch DVGS u.a. Berufsverbände (UK möglicherweise ein neuer Level 5 Instructor, durch die WRIGHT Foundation u.a. ausgebildet).

8 REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. (2010): American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*; 121:46-215.

2. NCHS (2013): Vital statistics of the United States - data from 2010. www.cdc.gov/nchs/data/dvs/deaths_2010_release.pdf; last accessed on 11.05.2013.

3. Lopez AD, Shibuya K, Rao C, et al. (2006): Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J*; 27: 397-412.

4. Böhm M. (2002): Pathophysiologie der Herzinsuffizienz heute. Herz, 27: 75-90.

5. Remme WJ, Swedberg K (2001): Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*, 22: 1527-1560.

6. Opasisch C, Ambrosino N, Felicetti G, et al. (1999): Heart failure-related myopathy: clinical and pathophysiological insights. *Eur Heart J*, 20: 1191-1200.

7. Volterrani M, Clark AL, Ludman PF, Swan JW, et al. (1994): Predictors of exercise capacity in chronic heart failure. *Eur Heart J*, 18: 801-809.

8. Drexler H, Funke E, Riedle U (1991): The oxydative enzyme activity decreases in all fibre types in skeletal muscle of patients with chronic heart failure. *Circulation*, 86: 11-74.

9. Mancini DM, Henson D, La Manca J, Levine S (1992): Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation*, 86: 909-918.

10. Mancini DM, Walther G, Reichek N, et al. (1992): Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation*, 85: 1364-1373.

11. Sullivan M, Gree H, Cobb FR (1990): Altered skeletal muscle response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. *Circulation*, 84: 1597-1607.

12. Dubach P, Myers J, Dziekan G, et al. (1997): Effect of high intensity training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol*, 29: 1591-1598.

13. Keteyian S, Levine AB, Brawner CA, Kataoka T, et al. (1996): Exercise training in patients with chronic heart failure. *Ann Intern Med*, 124: 1051-1057.

14. Meyer K, Schwaibold M, Westbrook S, Beneke R, et al. (1997): Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. *Am Heart J*, 133: 447-453.

15. Nechwatal RM, Duck C, Gruber G (2002): Körperliches Training als Intervall- oder kontinuierliches Training bei chronischer Herzinsuffizienz zur Verbesserung der funktionellen Leistungskapazität, Hämodynamik und Lebensqualität – eine kontrollierte Studie. *Z Kardiol*, 91: 328-337.

16. Stratton JR, Dunn JF, Adamopoulus S, et al. (1994): Training partially reverses skeletal muscle metabolic abnormalities during exercise in heart failure. *J of Appl Physiol*, 76, 1575-1582.

17. Wielenga RP, Huisveld IA, Bol E, et al. (1999): Safety and effects of physical training in chronic heart failure. *Eur Heart J*, 20: 872-879.

18. Gordon A, Tyni-Lenné R, Persson H, et al. (1996): Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiology*. 19: 568-574.

19. Hambrecht R, Gielen S, Linke A, et al. (2000): Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA*, 283: 3095-3101.

20. Magnusson G, Gordon A, Kaijser L, et al. (1996): High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J*, 17: 1048-1055.

21. Fletcher MJ, Upton J, Taylor-Fishwick J, Buist SA, et al. (2011): COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease on a working age population. *BMC Public Health*; 11:612.

22. Ruff LK, Volmer T, Nowak D, Meyer A (2000): The economic impact of smoking in Germany. *Eur Respir J;* 16: 385-90.

23. British Healthcare Commission Clearing the air (2006): a national study of chronic obstructive pulmonary disease. *Healthcare Commission*.

24. Vogelmeier C, Buhl R, Gillissen A, et al. (2007): Guidelines for the Diagnosis and Therapy of COPD - Issued by Deutsche Atemwegsliga and Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin. *Pneumologie*; 61: 1-40

25. Würtemberger G, Bastian K. (2001): Funktionelle effekte unterschiedlicher trainingsformen bei patienten mit COPD. *Pneumologie* 55: 553-62.

26. Jakobsson P, Jorfeldt L, Brundin A (1990): Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD) with and without chronic respiratory failure. *Eur Respir J*; 3: 192–196.

27. Hildebrand IL, Sylven C, Esbjornsson M, Hellstrom K, Jansson E (1991): Does chronic hypoxaemia induce transformationsof fibre types? *Acta Physiol Scand*; 141: 435–439.

28. Gosker HR, Zeegers MP, Wouters EF, Schols AM (2007): Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax*; 62: 944-949.

29. Larsen AI, Lindal S, Aukrust P, Toft I, Aarsland T, Dickstein K (2002): Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity. *Int J Cardiol*; 83: 25-32.

30. Jagoe RT, Engelen MPKJ (2003): Muscle wasting and changes in muscle protein metabolism in chronic obstructive pulmonary disease. *Eur Respir J*; 22: Suppl. 46, 52–63.

31. Attanasio P, Anker SD, Doehner W, von Haehling S (2011): Hormonal consequences and prognosis of chronic heart failure. *Curr Opin Endocrinol Diabetes Obes*; 18:224-30.

32. Smart NA, Steele M (2011): The effect of physical training on systemic pro-inflammatory cytokine expression in heart failure patients: a systematic review. *Congest Heart Fail*; 17: 110-14.

33. Agapitou V, Dimopoulos S, Kapelios C, et al. (2013): Hormonal imbalance in relation to exercise intolerance and ventilatory inefficiency in chronic heart failure*. J Heart Lung Transplant*; 32: 431-36.

34. AACVPR (2004): Guidelines for cardiac rehabilitation and secondary prevention programs. 4th edition; Human Kinetics. Champaign IL, U.S.A.

35. Statistisches Bundesamt: Statistische Jahrbuch 2012. www.destatis.de/DE/ Publikationen/statistischesJahrbuch/GesellschaftundStaat/Gesundheit.pdf? blob=publicationFile (last accessed 16.052012).

36. Lopez-Sendon J (2011): The heart failure epidemic. In: Medicographia 109 - Heart failure today: a paradigm shift. 33(4): 363-369.

37. Rodeheffer RJ (2003): The new epidemiology of heart failure. *Curr Cardiol Rep*; 5 (3):181-186.

38. British Heart Foundation (2010): Coronary heart disease statistics. http://www.bhf.org.uk/research/heart-statistics.aspx (last accessed 23.05.2013).

39. AHA (2009): Heart disease and stroke statistical-update. Dallas: *American Heart Association*.

40. Vasan RS, Levy D (1996): The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. Arch Intern Med; 156(16):1789-96.

41. Davis JO (1995): An extra-adrenal sodium-retaining factor in congestive heart failure. *J Card Failure*; 1: 179-82.

42. Cahalin LP (1996): Heart failure. *Phys Therapy*; 76: 516-533.

43. European Society of Cardiology (2008): ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*; 29: 2388-2442.

44. Pauwels RA, Busit AS, Calverley PMA, et al. (2001): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 163: 1256-1276.

45. NCHS (2013): Vital statistics of the United States - data from 2010. www.cdc.gov/nchs/data/dvs/deaths_2010_release.pdf; last accessed on 11.05.2013.

46. Global Initiative for Chronic Obstructive Lung Disease [GOLD] (2013): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. www.goldcopd.org (last accessed 16.05.2013).

47. British Healthcare Commission (2006): Clearing the air - a national study of chronic obstructive pulmonary disease. *Healthcare Commission*. London, UK.

48. Vogelmeier C, Buhl R, Gillissen A, et al. (2007): Guidelines for the Diagnosis and Therapy of COPD - Issued by Deutsche Atemwegsliga and Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin. *Pneumologie*; 61: 1-40

49. Lingner H, Schwartz FW, Schultz K (2007): Volkskrankheit Asthma/COPD. Bestandsaufnahme und Perspektiven. Berlin, Heidelberg: Springer-Verlag Berlin Heidelberg.

50. Fletcher MJ, Upton J, Taylor-Fishwick J, Buist SA et al. (2011): COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease on a working age population. *BMC Public Health*; 11: 612.

51. Glaab T, Hohlfeld J M, Jörres R A, et al. (2006): Pathomechanismen der chronisch-obstruktiven Lungenerkrankung (COPD). *Med Klin*; 101: 951–956.

52. Lundbäck B, Lindenberg A, Lindström M, et al. (2002): Not 15 But 50% of smokers develop COPD? Report from the Obstructive Lung Disease in Northern Sweden Studies. *Resp Med*; 97: 115–122.

53. NICE clinical guideline 101 (2010): Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. www.guidance.nice.org.uk/cg101 (last accessed 17.05.2013).

54. Barnes PJ, Celi BR (2009): Systemic manifestations and comorbidities of COPD. *Eur Respir J*; 33: 1165-1685.

55. Barnes PJ, Shapiro SD, Pauwels RA (2003): Chronic obstructive pulmonary disease - molecular and cellular mechanisms. *Eur Respir J*; 22: 672-688.

56. Hjalmarsen A, Asebo U, Aakvaag A, Jorder R (1996): Sex hormone responses in healthy Men and male patients with COPD during oral glucose load. *Scand J Clin Lab Invest*; 56: 635-40.

57. Kamischke A, Kemper DE, Castel MA, Lüthke M, Rolf C, Behre HM, Magnussen H, Nieschlag E. (1998): Testosterone levels in men with COPD with or without glucocorticoid therapy. *Eur Respir J ;* 11: 41-45.

58. Korneiko AG, Sivachenko TP, Mechev DS, Dz'Òrdzo JP (1989) : Concentration of sex hormones in chronic bronchitis in men. *Vrach Delo*; 2: 38-39.

59. Creutzberg EC, Wouters EF, Mostert R, et al. (2003): A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest*; 124: 1733–42.

60. Burdet L, de Muralt B, Schutz Y, et al. (1997): Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med*; 156: 1800–1806.

61. Jakobsson P, Jorfeldt L, Brundin A (1990): Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD) with and without chronic respiratory failure. *Eur Respir J*; 3: 192–196.

62. Hildebrand IL, Sylven C, Esbjornsson M, Hellstrom K, Jansson E (1991): Does chronic hypoxaemia induce transformationsof fibre types? *Acta Physiol Scand*; 141: 435–439.

63. Gosker HR, Zeegers MP, Wouters EF, Schols AM (2007): Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax*; 62: 944-49.

64. Larsen AL, Lindal S, Aukrust P, Toft I, Aarsland T, Dickstein K (2002): Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity. *Int J Cardiol*; 83(1): 25-32.

65. Kuzma AM, Meli Y, Meldrum C, et al. (2008): Multidisciplinary Care of the Patient with Chronic Obstructive Pulmonary Disease. *The Proceedings of the Am Thora Society;* 5: 567-571.

66. Schols AM, Broekhuizen R, Weling-Scheepers CA, et al. (2005): Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr*; 82: 53-59.

67. Fletcher C, Peto R (1977): The natural history of chronic airflow obstruction. *BMJ*; 1(6077):1645-1648.

68. British Heart Foundation: Factsheet. www.bhf.org.uk/hearthealth; (last accessed 20.04.13).

69. Shanmugan G, Le´gare´ JF (2208): Revascularization for ischemic cardiomyopathy. *Curr Opin Cardio*; 23:148–152.

70. Anthonisen NR, Wright EC, Hodgkin JE, et al. (1986): Prognosis in chronic obstructive pulmonary disease. *Am Rev Resp Disease*;133: 14–20.

71. Burrows B, Bloom JW, Traver GA, et al. (1987): The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med*;317:1309–14.

72. Deutsche Vereinigung für Gesundheitssport und Sporttherapie - DVGS (2013): Definition of exercise therapy. http://www.dvgs.de/index.php?article_id=38&clang=1 (last accessed 25.05.2013).

73. Medical dictionary (2013): Definition of Rehabilitation. www.medical-dictionary.thefreedictionary.com/Rehabilitation (last accessed 26.05.2013).

74. Pauwels RA, Buist AS, Calverley PM et al. (2001): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*;163(5): 1256–1276.

75. McGavin CR, Gupta SP, McHardy GJR (1976): Twelve minute walking test for assessing disability in chronic bronchitis. *BMJ*; 1: 822–823.

76. Cockcroft A, Beaumont A, Guz A (1985): Effect of exercise training on walking distance, exercise ventilation andbreathlessness in patients with COAD. *Clin Sc*; 69(12): 7.

77. Adams J, Cline M, Reed M, et al. (2006): Importance of resistance training for patients after a cardiac event. *Proc (Bayl Univ Med Cent)*; 19(3): 246-248

78. Drexler H, Funke E, Riedle U (1991): The oxydative enzyme activity decreases in all fibre types in skeletal muscle of patients with chronic heart failure. *Circulation*, 86: 11-74.

79. Mancini DM, Henson D, La Manca J, Levine S (1992): Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation*, 86: 909-918.

80. Mancini DM, Walther G, Reichek N, Lenkinski R, McCully KK, Mullen JL, Wilson JR (1992): Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation*, 85: 1364-1373.

81. Sullivan M, Gree H, Cobb FR (1990): Altered skeletal muscle response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. *Circulation*, 84: 1597-1607.

82. World Health Organisation (1993): Needs and action priorities in cardiac rehabilitation and secondary prevention in patients with CHD. Geneva: World Health Organization. http://whqlibdoc.who.int/euro/-1993/EUR_ICP_CVD_125.pdf (last accessed 22.05.2013).

83. Piepoli MF, Flather M, Coats AJ (1998): Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial. *Eur Heart J*; 19:830–841.

84. Smart N, Marwick TH (2004): Exercise training for patients with heart failure - a systematic review of factors that improve mortality and morbidity. *Am J Med*; 116: 693–706.

85. Piepoli MF, Davos C, Francis DP, Coats AJ (2004): Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ*; 328: 189.

86. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S (2204): Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev*; 3: 3331.

87. Brodie D, Bethell H, Breen S (2006): Cardiac rehabilitation in England: a detailed national survey. Eur J Cardiovasc Prev Rehabil;13(1): 122-128.

88. Dubach P, Myers J, Dziekan G, et al. (1997): Effect of high intensity training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol*; 29(7): 1591-1598.

89. Keteyian S, Levine AB, Brawner CA, et al. (1996): Exercise training in patients with chronic heart failure. *Ann Intern Med*; 124: 1051-1057.

90. Meyer K, Schwaibold M, Westbrook S, et al. (1997): Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. *Am Heart J*; 133(4): 447-453.

91. Nechwatal RM, Duck C, Gruber G (2002): Körperliches Training als Intervall- oder kontinuierliches Training bei chronischer Herzinsuffizienz zur Verbesserung der funktionellen Leistungskapazität, Hämodynamik und Lebensqualität – eine kontrollierte Studie. *Z f Kardiol*; 91(4): 328-337.

92. Stratton JR, Dunn JF, Adamopoulus S, et al. (1994): Training partially reverses skeletal muscle metabolic abnormalities during exercise in heart failure. *J Appl Physiol*; 76: 1575-1582.

93. Wielenga RP, Huisveld IA, Bol E, et al. (1999): Safety and effects of physical training in chronic heart failure. *Eur Heart J*; 20(12): 872-879.

94. Gordon A, Tyni-Lenné R, Persson H, et al. (1996): Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiol*; 19(7): 568-574.

95. Hambrecht, R., Gielen, S., Linke, A., Fiehn, E., Yu, J., Walther, C., Schoene, N. & Schuler, G. (2000). Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA*; 283(23): 3095-3101.

96. Magnusson G, Gordon A, Kaijser L, et al. (1996): High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J,* 17, 1048-1055.

97. Belardinelli R, Georgiou D, Cianci G, Purcaro A (1999): Randomised, controlled trial of long-term moderate exercise training in chronic heart failure. *Circulation;* 99: 1173-1182.

98. Adamopoulos S, Parissis JT, Kremastinos DT (2003): New aspects for the role of physical training in the management of patients with chronic heart failure. *Int J Cardiol;* 90 (1): 1-14.

99. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L (2003): Anti-remodelling effect of long-term exercise training in patients with stable chronic heart failure: results of the exercise in left ventricular dysfunction and chronic heart failure (ELVD-CHF) trial. *Circulation;* 108 (5): 554-559.

100. Deutsche Gesellschaft für Prävention und Rehabilitation von Herzkreislauferkrankungen (2007): Deutsche Leitlinien zur Rehabilitation von Patienten mit Herz-Kreislauferkrankungen. *Clin Res Cardiol*; Suppl 3.

101. Deutsche Herzstiftung (Edit.) (2000): Chronische Herzschwäche. Frankfurt. Deutscher Ärzte- Verlag.

102. Association of the Chartered Physiotherapists Interested in Cardiac Rehabilitation (ACPICR) (2009): Standards for the Exercise Component of the Phase III Cardiac Rehabilitation. The Chartered Society of Physiotherapy, London.

103. O'Connor GT, Collins R, Buring JE, Yusuf S, et al. (1989): Rehabilitation with exercise after myocardial infarction. *Circulation*; 82: 234-224.

104. Van der Meer S, Zwerink M, van Brussel M, et al. (2012): Effect of outpatient exercise training programmes in patients with chronic heart failure: a systematic review. *Eur J Prev Cardiol*; 19(4): 795-803.

105. Davies EJ, Moxham T, Rees K, et al. (2010): Exercise based rehabilitation for heart failure. *Cochrane Database Systema Rev*, 4: CD003331.

106. Van Tol BA, Huijsmans RJ, Kroon DW, et al. (2006): Effects of exercise training on cardiac performance, exercise capacity and quality of life in

patients with heart failure: a meta-analysis. *J Heart Failure*; 8(8): 841-850.

107. Meyer K (2001): Exercise training in heart failure - recommendations based on current research. *Med Sci Sports Exerc;* 33(4):525-31.

108. Willenheimer R, Rydberg E, Cline C, et al. (2001): Effects on quality of life, symptoms and daily activity 6 months after termination of an exercise training Programme in heart failure patients. *Int J Cardiol;* 77 (1): 25-31.

109. Meyer K, Bückling J (2004): Exercise in heart failure: should aqua therapy and swimming be allowed? *Med Sci Sports Exerc*; 36(12): 2017-2023.

110. Belardinelli R, Georgiou D, Cianci G, Purcaro A (1999): Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*; 99(9): 1173-1182.

111. Kiilavuori K, Näveri H, Salmi T, Härkönen M (2000): The effect of physical training on skeletal muscle in patients with chronic heart failure. *Eur J Heart Fail*; 2(1):53-63.

112. Larsen AI, Lindal S, Aukrust P, Toft I, Aarsland T, Dickstein K (2002): Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity. *In J Cardiol*; 83(1): 25-32.

113. Gielen S, Sandri M, Kozarez I, et al. (2012): Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age: the randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging catabolism study. *Circulation*; 125(22): 2716-27.

114. Westhoff TH, Schmidta S, Grossa V, Joppkea M, Zideka W, (2008) The Cardiovascular Effects of Upper-Limb Aerobic Exercise in Hypertensive Patients. *J Hyperten;* 26(7): 1-8.

115. Amos K, Porcari JP, Bauer S, Wilson P (1992): The safety and effectiveness of walking with ankle and wrist weights in cardiac rehabilitation patients. *J Cardiopul Rehabil;* 12(4): 254-260.

116. Franklin BA (1985): Exercise testing, training and arm ergometry. *Sport Med*; 2: 100-119.

117. American Association of Cardiovascular and Pulmonary Rehabilitation (2006): Cardiac Rehabilitation Resource Manual. Champaign, IL: Human Kinetics.

118. Meyer K, Samek L, Schwaibold M, et al. (1997): Interval training in patients with severe chronic heart failure - Analysis and recommendations for exercise procedures. *Med Sci Sport Exerc;* 29: 306-312.

119. Willenheimer R, Erhardt L, Cline C, et al. (1998): Exercise training in heart failure improves quality of life and exercise capacity. Eur Heart J; 19(5):774-81.

120. Nechwatal RM, Duck C, Gruber G (2002):Physical training as interval or continuous training in chronic heart failure for improving functional capacity, hemodynamics and quality of life--a controlled study. Z Kardiol; 91(4):328-37.

121. Pina IL, Apstein CS, Balady GJ, et al. (2003): Exercise and Heart Failure - A Statement From the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation;* 107: 1210-1225.

122. Daub WD, Knapik GP, Black WR (1996): Strength training early after myocardial infarction. *J Cardiopulm Rehabil*; 16: 100-108.

123. Dennis C, Houston-Miller N, Schwartz RG, et al. (1988): Early return to work after uncomplicated myocardial infarction. *JAMA*; 260: 214-220.

124. McCartney N (1999): Acute responses to resistance training and safety. *Med Sci Sports Exerc*; 31: 31–37.

125. McCartney N, McKelvie RS (1996): The Role of Resistance Training in Patients with Cardiac Disease. *Eur J Cardiov Prev & Rehab*; 3(2): 160-166.

126. Bjarnason-Wehrens B, Mayer-Berger W, Meister ER, et al. (2004): Recommendations for resistance exercise in cardiac rehabilitation. Recommendations of the German Federation for Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*; 11(4): 352-361.

127. Braith RW (1998): Exercise training in patients with CHF and heart transplant recipients. *Med Sci Sports Exerc*; 30(10): 367-378.

128. Featherstone JF, Holly RG, Amsterdam EA. (1993) Physiologic responses to weight lifting in coronary artery disease. *Am J Cardiol*.;71: 287–292.

129. Adams J, Cheng D, Berbarie RF (2013): High-intensity, occupation-specific training in a series of firefighters during phase II cardiac rehabilitation. *Proc (Bayl Univ Med Cent);* 26(2):106-118.

130. Karlsdottir AE, Foster C, Porcari, JP, et al. (2002): Hemodynamic Responses dur. Aerobic & Resistance Exercise. *J Cardpul Rehab*. 22(3): 170-177.

131. Mandic S, Myers J, Selig SE, Levinger I (2012): Resistance vs. aerobic exercise training CHF. *Curr Heart Fail Rep*; 9(1): 57-64.

132. Heyward, V (2010): Advanced Fitness Assessment and Exercise Prescription. 6th Ed. *Human Kinetics*. Champaign, Ilinois.

133. Ewart, C. K. Psychological effects of resistive weight training: implications for cardiac patients. *Med. Sci. Sports Exerc. 21:683-688, 1989.*

134. Haennel RG, Quinney HA, Kappagoda CT (1991): Effects of hydraulic circuit training following coronary artery bypass surgery. *Med Sci Sports Exerc*; 23(2):158-165.

135. Wielenga RP, Erdman RA, Huisveld IA, et al. (1998): Effect of exercise training on quality of life in patients with chronic heart failure. J Psychosom Res; 45(5):459-64.

136. Maiorana A, O'Driscoll G, Cheetham C, et al. (2000): Combined aerobic & resistance exercise training improves functional capacity and strength in CHF. *Appl Physiol;* 88: 1565–1570.

137. Laoutaris ID, Adamopoulos S, Manginas A, et al. (2012): Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? *Int J Cardiol*; (Epub ahead of print).

138. Oldbridge NB, Connolly C (1989): Oxygen uptake & heart rate during cross-country skiing & track walking after myocardial infarction. *Am Heart J*; 117: 495-497.

139. Smart NA, Steele M (2011): The effect of physical training on systemic pro-inflammatory cytokine expression in heart failure patients: a systematic review. Congest Heart Fail; 17(3): 110-114.

140. Cassaburi R, Porszaz J, Mary R, et al. (1997): Physiological benefits of exercise training with severe COPD. *Am Respir Crit Care Med;* 155: 1541-1551.

141. American Thoracic Society (1999): Pulmonary rehabilitation. *Am J Respir Crit Care Med*; 159: 1666–1682.

142. Donohue JF, van Noord JA, Bateman ED et al. (2002): 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest*; 122:47–55.

143. Barr RG, Bourbeau J, Camargo CA, Ram FSF (2005): Tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, Issue 2.

144. Rabe KF, Bateman ED, O'Donnell D et al. (2005): Roflumilast-an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*; 366: 563–71.

145. Celli BR, MacNee W (2004): Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*; 23: 932–946.

146. American Thoracic Society. Pulmonary rehabilitation (1999). *Am J Respir Crit Care Med;* 159: 1666–1682.

147. Troosters T, Gosselink R, Decramer M (2000): Short-and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med*;109(3): 207–212.

148. Brooks D, Krip B, Mangovski-Alzamora S, Goldstein RS (2002): The effect of post-rehabilitation programmes among individuals with chronic obstructive pulmonary disease. *Eur Respir J*; 20(1): 20–29.

149. Ries AL, Kaplan RM, Myers R, Prewitt LM (2003): Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med*; 167(6): 880–888.

150. Pauwels RA, Buist AS, Calverley PM et al. (2001): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*; 163(5): 1256–1276.

151. American College of Sports Medicine (2010): ACSM current comment - Exercise for persons with chronic obstructive pulmonary disease. Indianapolis, USA.

152. Deutsche Gesellschaft fur Pneumologie & Beatmungsmedizin/RGRW (2007): Rehabilitation of Patients with Chronic Obstructive Pulmonary Disease (COPD) - S2 Guideline of the German Society for Pneumology and Respiratory Medicine and the German Society for Rehabilitation Science (RGRW). *Pneumologie*; 61: 233-248.

153. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, et al. (2007): Pulmonary Rehabilitation Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest;* 131(5): 38-42.

154. Troosters T, Cassaburi R, Gosselink R, Decrammer M (2005): Pulmonary rehabilitation in COPD. *Am J Respir Crit Care Med;* 172(9): 19-38.

155. Punzal PA, Ries AL, Kaplan RM et al. (1991): Maximum intensity exercise training in patients with chronic obstructive pulmonary disease . *Chest;* 100: 618-623.

156. Strijbos JH, Postma DS, van Altena R et al. (1996:) A comparison between an outpatient hospital -based pulmonary rehabilitation program and a home-based pulmonary rehabilitation program in patients with COPD. *Chest;* 36-72.

157. Bernard S, Whittom F, Leblanc P, et al. (1999): Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med; 159(3):896-901.

158. Vogialtiz I, Nanas S, Roussos C (2002): Interval training as an alternative modality to continuous exercise in patients with COPD. A randomised clinical trial. *Eur Respir Journal.* 20 12-19.

159. Rooyackers JM, Berkelion DA, Folgering HT (2003): Eccentric exercise training in patients with COPD. A randomised clinical trial. *Int J Rehabil Res;* 26: 47-49.

160. O'Donnell DE, Lam M, Webb KA (1998): Measurements of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive. *Am J Respir Crit Care Med,* 158(5): 1557-1565.

161. Vogiatzis I, Terzis G, Nanas S, et al. (2005): Skeletal Muscle Adaptations to Interval Training in Patients with Advanced COPD. *Chest;* 128(6): 3838-3845.

162. Beauchamp MK, Nonyama M, Goldstein RS, et al. (2010): Interval versus continuous training in individuals with chronic obstructive pulmonary disease- a systematic review. *Thorax;* 65: 157-164.

163. Kortianou E, Nasis IG, Spetsioti ST et al. (2010): Effectiveness of Interval Exercise Training in Patients with COPD. *Cardiopul Phys Therapy J*; 21(3): 12-19.

164. Phillips WT, Benton MJ, Wagner CL, Riley C (2007): The Effect of Single Set Resistance Training on Strength and Functional Fitness in Pulmonary Rehabilitation Patients. *J Cardiopulmon Rehab;* 26: 330-337.

165. Semple SJ, McKune AJ (2007): COPD - Is there evidence to support a role for resistance training in improving measurable health-related quality of life in pulmonary rehabilitation? *South Afric J Sports Med;* 19(5): 108-113.

166. Nelson ME, Rejeski WJ, Blair SN, et al. (2007): Physical activity and public health in older adults - Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation;116*(9): 1094-1105.

167. Langer D, Hendriks E, Burtin C, et al. (2009): A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehab; 23*(5): 445-462.

168. O'Shea SD, Taylor NF, Paratz J (2004): Peripheral muscle strength training in COPD- A systematic review. *Chest; 126*(3): 903-914.

169. Vogiatzis I (2011): Strategies of muscle training in very severe COPD patients. *Eur Respir J;* 7: 750-811.

170. Reis LF, Guimaraes FS, Fernandes SJ, et al. (2013): A long-term pulmonary rehabilitation program progressively improves exercise tolerance, quality of life and cardiovascular risk factors in patients with COPD. Eur J Phys Rehab Med; Epub ahead of print.

171. Diaz O, Villafranca C, Ghezzo H, ey al. (2000): Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Resp J*; 16( )2: 269-275.

172. Leith DE, Bradley M. (1976): Ventilatory muscle strength and endurance training. Journal of Applied Physiology; 41:508 - 516.

173. Gosseling R, De Vos J, van den Heuvel SP, et al. (2011): Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J*; 37: 416–425.

174. Vogiatzis I, Zakynthinos SG (2013): The physiological Basis of Rehabilitation in Chronic Heart and Lung Disease. J Appl Physiol; 25: Epub ahead of print.

175. Opasisch C, Ambrosino N, Felicetti G, et al. (1999): Heart failure-related myopathy: clinical and pathophysiological insights. *Eur Heart J;* 20: 1191-1200.

176. Volterrani M, Clark AL, Ludman PF, et al. (1994): Predictors of exercise capacity in chronic heart failure. *Eur Heart J*, 18: 801-809.

177. Drexler H, Funke E, Riedle U (1991): The oxydative enzyme activity decreases in all fibre types in skeletal muscle of patients with chronic heart failure. *Circulation;* 86: 11-74.

178. Mancini DM, Henson D, La Manca J, Levine S (1992): Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation;* 86: 909-918.

179. Mancini DM, Walther G, Reichek N, et al. (1992): Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation;* 85: 1364-1373.

180. Sullivan M, Gree H, Cobb FR (1990): Altered skeletal muscle response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. *Circulation;* 84: 1597-1607.

181. Dubach P, Myers J, Dziekan G, Goebbels U, et al. (1997): Effect of high intensity training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol*; 29(7): 1591-1598.

182. Keteyian S, Levine AB, Brawner CA, et al. (1996): Exercise training in patients with chronic heart failure. *An Intern Med*; 124: 1051-1057.

183. Meyer K, Schwaibold M, Westbrook S, et al. (1997): Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. *Am Heart J*; 133 (4): 447-453.

184. Nechwatal RM, Duck C, Gruber G (2002): Körperliches Training als Intervall- oder kontinuierliches Training bei chronischer Herzinsuffizienz zur Verbesserung der funktionellen Leistungskapazität, Hämodynamik und Lebensqualität – eine kontrollierte Studie. *Z Kardiol*; 91(4): 328-337.

185. Stratton JR, Dunn JF, Adamopoulus S, et al. (1994): Training partially reverses skeletal muscle metabolic abnormalities during exercise in heart failure. *J Appl Physiol;* 76: 1575-1582.

186. Wielenga RP, Huisveld IA, Bol E, et al. (1999): Safety and effects of physical training in chronic heart failure. *Eur Heart J*; 20(12): 872-879.

187. Gordon A, Tyni-Lenné R, Persson H, et al. (1996): Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiol*; 19(7); 568-574.

188. Hambrecht R, Gielen S, Linke A, et al. (2000): Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA*; 283(23): 3095-3101.

189. Magnusson G, Gordon A, Kaijser L, et al. (1996). High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J*; 17: 1048-1055.

190. Gielen S, Adams V, Mobius-Winkler S, et al. (2003): Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardio;* 42(5): 869-872.

191. Hambrecht R, Schulze PC, Linke A, et al. (2000). Effects of exercise training on local expression of insulin-like growth factor-1 in the skeletal muscle of patients with chronic heart failure. *Circulation;* 102: 411-413.

192. Hambrecht R, Wolff A, Gielen S, et al. (2000): Effect of exercise on coronary endothelial function in patients with coronary heart disease. *N Engl J Med;* 342: 454-460.

193. Linke A, Schoene N, Gielen S, et al. (2001): Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. *J Am Coll Cardiol*; 37: 392-397.

194. Braith R, Welsch M, Kluess HA, Pepine C (1999):. Neuro endocrine activation in heart failure is modified by endurance training. *J Am Coll Cardiol;* 34: 1170-1175.

195. Barlow CW, Qayyum MS, Davey PP, et al. (1994): Effect of Physicial Training on exercised-induced Hyperkalemia in chronic heart failure. *Circulation;* 89(3): 1144-1152.

196. Belardinelli R, Georgiou D, Cianci G, Purcaro A (1999): Randomized, controlled trial of long-term moderate exercise training in chronic heart failure. *Circulation*; 99: 1173-1182.

197. Bertram R, Cordes S, Schmidt S, (2002): Trainings- und Schulungsmaßnahmen bei schwerer chonischer Herzinsuffizienz. Erfahrung und Umsetzung in der Praxis. *Med Klin*; 97(2): 57-62.

198. Coats AJS, Adamopoulos S, Meyer TE, et al. (1990): Effects of physical training in chronic heart failure. *Lancet;* 335: 63-66.

199. Coats AJS, Adamopoulos S, Radaelli A, et al. (1992): Controlled trial of physical training in chronic heart failure. *Circulation*; 85(6): 2119-2130.

200. Conraads V, Beckers P, Vaes J, et al. (2003): Combined endurance/resistance training reduces serum NT-proBNP in patients with moderate to severe chronic heart failure. *Eur J Cardiovasc Prev Rehab;* 10: 398.

201. Erbs S, Linke A, Gielen S, et al. (2003): Exercise training in patients with severe chronic heart failure impact on left ventricular performance and cardiac size. A retrospective analysis of the Leipzig heart failure training trial. *J Cardiovasc Risk*; 10(5): 336-344.

202. Gianuzzi P, Mezzani A, Saner H, et al. (2003): Physical activity for primary and secondary prevention. Position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. *Eur J Cardiovasc Prev Rehab*; 10: 319-327.

203. Gielen S, Adams V, Mobius-Winkler S, et al. (2003): Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*; 42(5): 869-872.

204. Gordon A, Tyni-Lenné R, Persson H, et al. (1996): Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiol*; 19(7): 568-574.

205. Grosse T, Kreulich K, Nägele H, et al. (2001): Peripheres Muskelkrafttraining bei schwerer Herzinsuffizienz. *Dtsch Z Sportmed*; 52(1): 11-14.

206. Hambrecht R, Gielen S, Linke A, et al. (2000): Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. *JAMA;* 283(23): 3095-3101.

207. Jetté M, Heller R, Landry F, Blümchen G (1991): Randomized 4-week exercise program in patients with impaired left ventricular function. *Circulation;* 84(4): 1561-1567.

208. Kavanagh T, Myers MG, Baigrie RS, et al. (1996): Quality of life and cardiorespiratory function in chronic heart failure: effect of 12 months´ aerobic training. *Heart;* 76: 42-49.

209. Keteyian S, Levine AB, Brawner CA, et al. (1996): Exercise training in patients with chronic heart failure. *An Internal Med*; 124: 1051-1057.

210. Meyer K, Laederach-Hofmann K (2003): Effects of a comprehensive rehabilitation program on quality of life in patients with chronic heart failure. *Prog Cardiovasc Nurs*; 18(4): 169-176.

211. Giallauria et al. (2008): Left ventricular remodelling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-brain natriuretic peptide. *Eur J Cardiovasc Prev Rehabil*; 15(1): 113-118.

212. Callaerts-Vegh et al. (1998): Influence of intensive physical training on urinary nitrate elimination and plasma endothelin-1 levels in patients with congestive heart failure. *J Cardiopulm Rehabil*; 18: 450–457.

213. Demopoulos et al. (1997): Exercise training in patients with severe congestive heart failure:enhancing peak aerobic capacity while minimizing the increase in ventricular wall stress. *J Am Coll Cardiol*; 29: 597–603.

214. Meyer K, Schwaibold M, Westbrook S, et al. (1997): Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. *Am Heart J;* 133(4): 447-453.

215. Meyer K, Samek L, Schwaibold M, et al. (1997): Predictors of response to exercise training in severe chronic congestive heart failure. *Am J Cardiol*; 80(1): 56-60.

216. Kellermann A, et al. (1990): Arm exercise training in the rehabilitation of patients with impaired ventricular function and heart failure. *Cardiology*; 77: 130–138.

217. Braith RW, Beck DT (2008): Resistance exercise: training adaptations and developing a safe exercise prescription. *Heart Fail Rev*; 13(1): 69-79.

218. Buskies W, Boeck-Behrens WU (2001): Gesundheitsorientiertes fitnesstraining. Lüneburg: Wehdemeier & Pusch.

219. Casaburi RA, Porszasz J, Burns M, Carithers ER, et al. (1997): Physiologic benefits of exercise training in rehabilitation of patients with severe chronic pulmonars disease. *Am J Respir Crit Care Med;* 155: 1541-51.

220. Coppoolse R, Schols AMWJ, Baarendes EM, et al. (1999): Interval versus continuous training in patients with COPD. *Eur Respir J* ; 14: 258-263.

221. Emtner M, Herala M, Stahlenheim C (1996): High-intensity physical training in adults with asthma. *Chest*; 109: 323-330.

222. Frontera WR, Meredith CN, O`Reilly KP, Evans WJ (1990): Strength training and determinants of VO_{2max} in older men. *J Appl Physiol;* 68: 329-333.

223. Hjalmarsen A, Asebo U, Aakvaag A, Jorder R (1996): Sex hormone responses in healthy Men and male patients with COPD during oral glucose load. *Scand J Clin Lab Invest;* 56:635-40.

224. Kamischke A, Kemper DE, Castel MA, et al. (1998): Testosterone levels in men with COPD with or without glucocorticoid therapy. *Eur Respir J*; 11: 41-45.

225. Korneiko AG, Sivachenko TP, Mechev DS, Dz'Òrdzo JP (1989) : Concentration of sex hormones in chronic bronchitis in men. *Vrach Delo;* 2: 38-39.

226. Viru A. (2000): Hormonelle veränderungen in der taper-phase unmittelbar vor einem wettkampf. *Leistungssport;* 7:4-8.

227. Hautzinger M, et al. (1994): Beck-Depression-Inventory (BDI). Test manual. Toronoto.

228. Heck H. (1998): Unpublished study. Fakultät für Sportwissenschaft, Lehrstuhl für Sportmedizin. Bochum.

229. Maltais F, Simrad C, Jobin J, Desgagnes P, Leblanc P (1996) : Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med*; 153: 288-293.

230. Leuppi JD, Zenhäusern, Schwarz F, Frey WO, Villiger B (1998): Bedeutung der trainingsintensität für die verbesserung der ausdauerleistungsfähigkeit bei patienten mit chronisch obstruktiven lungenerkrankungen. *Dtsch med Wschr*; 123: 174-178.

231. Diaz O, Villafranca C, Ghezzo H, ey al. (2000): Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Resp J*; 16( )2: 269-275.

232. Geddes EL, O'Brien K, Reid WD, et al. (2008): Inspiratory muscle training in adults with chronic obstructive pulmonary disease: An update of a systematic review. *Respir Med;* 102(12): 1715-1729.

233. Celli BR, MacNee W & ATS/ERS Task Force (2004): Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *Eur Respir J; 2*3(6): 932-946.

234. Ries AL (2008) Pulmonary rehabilitation: summary of an evidence-based guideline. *Respir Care*; 53(9): 1203-1207.

235. Gosseling R, De Vos J, van den Heuvel SP, et al. (2011): Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J*; 37: 416–425.

236. Guyatt G (2009): The chronic respiratory questionnaire – CRQ original. Backround information and interviewing suggestions. Hamilton: McMaster University.

237. Shoemaker MJ, Donker S, Lapoe A (2009): Inspiratory muscle training in patients with chronic obstructive pulmonary disease: the state of evidence. *Cardiopul Phys Therapy J*; 20(3): 5-15.

238. Polkey MI, Moxham J (2004): Improvement volitional tests of muscle function alone may not be adequate evidence that inspiratory muscle training is effective. *Eur Respir J*; 23(1): 5-6.

239. Geddes EL, O'Brien K, Reid WD (2005): Inspiratory muscle training in adults with COPD: a systematic review. *Respir Med*; 99(11): 1440-1458.

240. Lotters F, van Tol B, Kwakkel G, Gosselink R, (2002): Effects of controlled inspiratory muscle training in patients with COPD: A meta-analysis. *Eur Respis J*; 20(3): 570-576.

241. Le Jemtel TH, Padeletti M, Jelic S (2007): Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol*; 49:171–180.

242. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW (2005): Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J*;26:1887–1894.

243. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW (2006): Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail*; 8:706–711.

244. Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G (2007): The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Fail*; 9:942–948.

245. Opasisch C, Ambrosino N, Felicetti G, et al. (1999): Heart failure-related myopathy: clinical and pathophysiological insights. *Eur Heart J*, 20: 1191-1200.

246. Volterrani M, Clark AL, Ludman PF, Swan JW, et al. (1994): Predictors of exercise capacity in chronic heart failure. *Eur Heart J*, 18: 801-809.

247. Drexler H, Funke E, Riedle U (1991): The oxydative enzyme activity decreases in all fibre types in skeletal muscle of patients with chronic heart failure. *Circulation*, 86: 11-74.

248. Mancini DM, Henson D, La Manca J, Levine S (1992): Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation*, 86: 909-918.

249. Mancini DM, Walther G, Reichek N, et al. (1992): Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation*, 85: 1364-1373.

250. Sullivan M, Gree H, Cobb FR (1990): Altered skeletal muscle response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. *Circulation*, 84: 1597-1607.

251. Jakobsson P, Jorfeldt L, Brundin A (1990): Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD) with and without chronic respiratory failure. *Eur Respir J*; 3: 192–196.

252. Agapitou V, Dimopoulos S, Kapelios C, et al. (2013): Hormonal imbalance in relation to exercise intolerance and ventilatory inefficiency in chronic heart failure. *J Heart Lung Transplant*; 32: 431-36.

253. Hildebrand IL, Sylven C, Esbjornsson M, Hellstrom K, Jansson E (1991): Does chronic hypoxaemia induce transformationsof fibre types? *Acta Physiol Scand*; 141: 435–439.

254. Gosker HR, Zeegers MP, Wouters EF, Schols AM (2007): Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax*; 62: 944-949.

255. Larsen AI, Lindal S, Aukrust P, Toft I, et al. (2002): Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity. *Int J Cardiol*; 83: 25-32.

256. Maiorana A, O'Driscoll G, Cheetham C, et al. (2000): Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. *Appl Physiol;* 88: 1565–1570.

257. Smart NA, Steele M (2010): Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. *Int J Cardiol*; 140(3): 260-265.

258. McCartney N. (1998): Role of resistance training in heart disease. *Med Sci Sports Exerc;* 30: 396–402.

259. McKelvie RS, McCartney N, Tomlinson C, Bauer R, MacDougall JD (1995): Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol;* 76: 977–979.

260. Magnussen G, Gordon A, Kaijser L, et al. (1996): High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J;* 17: 1048–1055.

261. Klijn P, van Keimpemann A, Legemaat M, et al. (2013): Nonlinear Exercise Training in Advanced COPD is Superior to Traditional Exercise Training: a Randomized Trial. Am J Respir Crit Care Med; Epub ahead of print.

262. Vogiatzis I, Terzis G, Stratakos G, et al. (2011): Effect of pulmonary rehabilitation on peripheral muscle fibre remodelling in patients with COPD in GOLD stages II to IV. *Chest*; 140(3): 744-752.

263. Velosso M, do Nascimento NH, Gazotti MR, Jardim JR (2013): Evaluation of effects of shoulder girdle training on strength and performance of activities of daily living in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*; 8: 187-192.

264. Bernard S, Whittom F, Leblanc P, et al. (1999): Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*; 159(3): 896-901.

265. Wehr E, Pilz S, Boehm B,, et al. (2011): Low free tesosterone is associated with heart failure mortality in coronary angiography. Eur J Heart Fail; 13:482-488.

266. Coventry PA, Bower P, Keyworth C, et al. (2013): The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. PloS One; Epub ahead of print.

267. Lacasse Y, Goldstein R, Lasserson TJ, Martin S (2009): Pulmonary rehabilitation for chronic obstructive pulmonary disease (Review). *The Cochrane Library;* Issue 3. John Wiley & Sons (Publisher).

268. Foy CG, Rejeski WJ, Berry MJ, et al. (2001): Gender Moderates the Effects of Exercise Therapy on Health-Related Quality of Life Among COPD Patients. *Chest;* 119(1): 70-76.

269. Butts JF, Belfer MH, Gebke KB (2013): Exercise for patients with COPD: an integral yet underutilized intervention. Phys Sportsmed; 41(1):49-57.

270. Glaab T, Hohlfeld J M, Jörres R A, et al. (2006): Pathomechanismen der chronisch-obstruktiven Lungenerkrankung (COPD). *Med Klin*; 101: 951–956.

271. Brooks D, Lacasse Y, Goldstein RS (1999): Pulmonary rehabilitation programs in Canada: national survey. *Canad Respir J*; 6:55–63.

272. Levin LA, Perk J, Hedback B, et al. (1991): Cardiac rehabilitation- a cost analysis. *J Int Med;* 230: 427-434.