Effects of group-based high-intensity aerobic interval training in patients with chronic heart failure

The Norwegian Ullevaal model

Birgitta Blakstad Nilsson

Doctoral Thesis

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Ullevål University Hospital
University of Oslo
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Oslo, August 2009

Birgitta Blakstad Nilsson

Errata

Paper II

Page 1363, Table I, New York Heart Association class II/III in the control group should be “24/16”.

Paper III

Page 1222, Table I, New York Heart Association class II/III in the control group should be “24/16” and Ejection fraction in the rehabilitation group should be “30 ± 8%”.

Page 1223, Table 2, workload (W) in the Control Group, Time 2, should be “72±20”.

Abstract, page 1220, line 6-7 should be “The mean ejection fractions at baseline were 30 ± 8% in the exercise group and 31 ± 9% in the control group.”

Accidentally, is “Rehabilitation Group” used in Table 1, (Characteristic) instead of “Exercise Group” as in the rest of the paper.

Abbreviations

6MWT	six minute walk test
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BNP	B-type natriuretic peptide
CAD	coronary artery disease
CHF	chronic heart failure
EF	ejection fraction
ESC	European Society of cardiology
HR	heart rate
HRQL	health related quality of life
ITT	intent to treat
MLHFQ	Minnesota living with heart failure questionnaire
NT pro-BNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
RCT	randomized controlled trial
RPE	rate of perceived exertion
SD	standard deviation
UUH	Ullevaal University Hospital
VO_{2max}	maximal oxygen uptake
VO_{2peak}	peak oxygen uptake

List of papers

I Nilsson BB, Hellesnes B, Westheim A, Risberg MA.
Group-based aerobic interval training in patients with chronic heart failure: Norwegian Ullevaal Model.
Physical Therapy 2008;88 (4):523-535

II Nilsson BB, Westheim A, Risberg MA.
Effects of group-based high-intensity aerobic interval training in patients with chronic heart failure.
American Journal of Cardiology 2008; 102:1361-1365

III Nilsson BB, Westheim A, Risberg MA.
Long-term effects of a group-based high-intensity aerobic interval-training program in patients with chronic heart failure.
American Journal of Cardiology 2008; 102:1220-1224

IV Nilsson BB, Westheim A, Risberg MA, Arnesen H, Seljeflot I.
The effect of group-based aerobic interval training on N-terminal pro B-type natriuretic peptide levels in patients with chronic heart failure.
Submitted

INTRODUCTION

Chronic heart failure

Definition

Chronic heart failure (CHF) has many causes and a complex pathophysiology. A universally agreed upon definition is not to be found [1]. However, it can be defined as a progressive clinical syndrome in which the heart is unable to deliver enough blood to meet the demand of the peripheral organs, which results in symptoms of fatigue, dyspnea and fluid retention [2]. Fatigue and dyspnea may lead to decreased physical activity and limit functional capacity and health related quality of life (HRQL). Fluid retention may lead to pulmonary congestion and peripheral edema. The key components of CHF, according to the latest guidelines from the European Society of Cardiology (ESC), are the following [3]:

- Symptoms typical of CHF:

  dyspnea at rest or during exercise, fatigue, tiredness, ankle swelling

  AND
- Signs typical of CHF:

  tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly

  AND
- Objective evidence of structural or functional abnormality of the heart at rest

  abnormality on the echocardiogram, cardiomegaly, third heart sound, cardiac murmurs, raised natriuretic peptide levels.

Objective assessment based on objective measures of cardiac structure and function (e.g., ECG, chest x-ray, echocardiography, radiologic imaging, stress testing) is important to evaluate cardiac status in CHF. However, it is well-known that the severity of symptoms for patients with CHF is not necessarily matched with the degree of impaired structure and the functional limitation. CHF is additionally quantified by the New York Heart Association (NYHA) functional classification [4] (Table 1). This classification is not exact, but remains the most widely used grading system of common symptoms in patients with CHF [5].

Table 1. New York Heart Association (NYHA) functional classification of patients with chronic heart failure [5].

NYHA class	Symptoms	One year mortality
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.	5%
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpation, or dyspnea.	10-15%
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpation, or dyspnoea.	20-30%
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.	35-50%

The cardiac natriuretic hormones (peptides), B-type natriuretic peptide (BNP) or amino terminal pro B-type Natriuretic Peptide (NTpro-BNP) are increased in patients with CHF. These peptides are increasingly used in the prognosis and diagnosis of patients

with CHF, and differentiate CHF patients from patients with non-cardiac causes of acute dyspnea [6]. NT pro-BNP has emerged as a powerful circulating marker of cardiac function [7,8].

Prevalence, incidence and prognosis

CHF is a major and increasing health problem, and one of the main causes of death in the western society [9], with a prognosis equal to many highly malignant tumors [10]. The prevalence of CHF increases with age, from about 1-2 % in persons 25-75 years, up to 9-20 % in persons > 75 years [3,11,12]. CHF is the leading diagnosis for hospitalization of older adults [13]. It has been estimated that the number of CHF cases will double in the next four decades [14,15]. It seems like the prevalence of CHF is rising, because the incidence of older people in the population is increasing. In addition, improved treatment of coronary artery disease (CAD) means that more patients survive to develop CHF [16].

Causes

Almost all cardiac diseases can lead to CHF. The most frequent causes are often a long-term outcome of diseases such as myocardial infarction secondary to CAD, hypertension, valvular disease, arrhythmias, myocarditis and cardiomyopathies [3]. In addition, the syndrome can deteriorate due to e.g. anemia, thyrotoxicosis, cardiodepressant drugs and renal failure [4].

N-terminal pro B-type natriuretic peptide

The cardiac natriuretic hormones are a family of related peptide hormones produced by cardiac myocytes [17]. When released from cardiac myocytes, pro B-type peptide is cleaved into BNP and its N-terminal fragment, NT pro-BNP. BNP and NT pro-BNP levels in plasma reflect the stretch and tension of the myocardial wall [18]. This stretching of ventricular myocytes cause the production and release of the cardiac natriuretic hormones [8]. Plasma BNP and NT pro-BNP levels are also elevated in patients with pulmonary hypertension [19], in patients with renal dysfunction [20] in addition to patients with and without CHF who exhibit a high body mass index [21].

High levels of BNP and NT pro-BNP identify patients at greatest risk of future cardiovascular events, including death [22], but BNP and NT pro-BNP can not replace information obtained from echocardiography and invasive hemodynamic monitoring [18]. Adjusting medical therapy in patients with CHF in order to reduce natriuretic peptides levels may improve outcome [23]. In addition, exercise training may lead to a decrease in BNP and NT pro-BNP levels [24]. However, there are controversial results regarding the effect of exercise training on BNP and NT pro-BNP in patients with CHF [24-28].

Exercise training in patients with chronic heart failure

Patients with CHF have 30-50% reduced functional capacity as compared with age – matched healthy subjects [2,29]. A reduced functional capacity have shown to result in lower HRQL [30].

Until the 1990s, CHF was described as a condition best treated by rest, and patients with CHF were excluded from exercise training due to concerns of safety and

beneficial effects in an already damaged myocardium [31,32]. By contrast, the latest guidelines for diagnosis and treatment of CHF from the American Heart Association [33] and ESC [3,34], recommend exercise training for all patients with stable CHF. A number of studies from the last decades have led to this change in treatment approach [35-42].

Exercise training has been shown to be well tolerated in patients with stable CHF and has been shown to result in improved functional capacity and HRQL [42]. Evidence suggests that these benefits mainly are due to the effects of exercise training on peripheral skeletal muscles and circulation rather than on the myocardium [43]. In addition, exercise training has been shown to improve the ratio of type 1 and type 2 muscle fibers in skeletal muscles [44], partially reverse activation of the neurohormonal system, reduce levels of pro-inflammatory cytokines [44], reduce dependence on anaerobic metabolism [34], improve skeletal muscle metabolism [45], and increase blood flow within the active skeletal muscles [46]. There is limited evidence to support the contention that exercise training can lead to a reduction of mortality and morbidity in patients with CHF. Most of the studies employ a small sample size too small to be able to distinguish between no effect and a reduction of 20% in cardiovascular related mortality. A meta analysis by the ExTraMATCH Collaborative group [47] found that exercise training reduced mortality, morbidity and hospital admissions. The results of the ongoing HF-ACTION Trial [48] (an international, multi-centre, randomized trial) will provide long-awaited information about the effects of exercise training on mortality and morbidity in patients with CHF (EF<35%) in NYHA class II-IV.

There is no general agreement on exercise training mode or intensity for patients with CHF, probably due to the variation in the studies included in the exercise guidelines

[2,34]. The exercise training mode vary considerably in the literature and cycle ergometer and treadmills are most frequently used in exercise training programs [47]. Furthermore, individual tailored exercise training at moderate intensity are most frequently included in the previously published studies [39,42,49-53]. Research on an exercise training mode often used in Scandinavian hospitals and cardiac rehabilitation centre, group-based aerobic interval training (see Paper I) is limited. Recent research, however, suggest greater functional capacity and cardiovascular adaptations result from high intensity exercise training compared to low/moderate intensity both in healthy subjects [54], and in patients with CAD [55] and CHF [45].

Cardiac rehabilitation is described as an interdisciplinary intervention aimed at improving functional capacity, as well as psychological and social conditions affecting people with chronic or post-acute heart disease [56,57]. Exercise training therefore needs to include group and/or individual counseling to target the patients' psychological and social conditions [57]. Patients with CHF have a poorer HRQL than other common chronic conditions such as diabetes and chronic lung disease [58]. In accordance with the severity of symptoms in patients with CHF, patients develop severe psychological disorders, such as anxiety and depression [59]. There is conflicting evidence on the effect of exercise training on HRQL in patients with CHF [26,42], and no changes in HRQL were observed in the EXERT trial [60]. Therefore, HRQL should be included in an evaluation of exercise training programs for patients with CHF.

The overall aim of the exercise training is to encourage patients to maintain a physical active lifestyle following the exercise training prescription (exercise adherence). However, studies of exercise training for patients with CHF lack attention to the issue of

exercise adherence in these patients [61]. Only a few studies have evaluated exercise adherence in the long term (>12 months). An important factor by adherence to exercise training is to increase the patients self-efficacy [61]. Self-efficacy is a part of Bandura´s social learning theory [62], and it is characterized by four main components; observation of others, persuasion by an authority, successful performance of the behavior and physiologic feedback.

AIMS OF THE STUDY

The overall aim of the work presented in this thesis was to evaluate the effect of the Norwegian Ullevaal model (group-based high-intensity aerobic interval training including counseling) in patients with CHF on functional capacity, quality of life and circulating levels of NT pro-BNP. To achieve this, we evaluated the feasibility and effects of the Norwegian Ullevaal model and designed a randomized controlled trial, following patients with CHF for 12 months.

The specific aims were:

Paper I

- To describe the Norwegian Ullevaal model for patients with CHF in NYHA class III.
- To evaluate if the program was feasible for this patient group, and to describe how the program was developed and implemented as an interdisciplinary treatment program.

Paper II

- To evaluate the effect of the Norwegian Ullevaal model on functional capacity in patients with CHF, compared to a control group who received standard care.
- To evaluate the differences in HRQL in patients with CHF who had received the intervention program compared to the control group.

- To examine the relationship between changes in functional capacity and HRQL.

Paper III

- To evaluate the long-term effect (12 months follow-up) of the Norwegian Ullevaal model on functional capacity and HRQL in patients with CHF compared to a control group.

Paper IV

- To evaluate the effect of the Norwegian Ullevaal model on circulating levels of NT pro-BNP in patients with CHF.
- To examine the relationship between NT pro-BNP and functional capacity.

MATERIAL AND METHODS

Four papers were included in this thesis. Paper I is a case report and Papers II, III and IV are randomized controlled trials based on data from one study sample.
The majority of the protocol is presented in Paper II, and the Norwegian Ullevaal model is in detail described in Paper I. Therefore, the protocol is only briefly described.

Patients

From September 2001 until February 2004, 80 patients (63 men and 17 women), with CHF in NYHA class II-IIIB, were included. All patients who were referred to the heart failure out-patient clinic at Ullevaal University Hospital (UUH) in Oslo, and who met the inclusion criteria, were invited to participate in the study. In addition from September 2003, we invited patients from the heart failure out-patient clinic at Lovisenberg Hospital, Oslo, into the study.

Prior to assess them for eligibility to the study (screening), all patients had been titrated to maximal tolerable doses of medical treatment at the heart failure out-patient clinic (standard care). After optimal medical treatment, all patients underwent a six minute walk test (6MWT) as a screening test before inclusion. After baseline testing, patients were consecutively randomized to either the exercise group or the control group by a permuted block randomization (the block size was 4), provided by Center for Clinical Research at UUH (Figure 1). The four patients described in the case report (Paper I) were four random patients with CHF in NYHA class III who were included in the intervention group of the study.

Inclusion criteria:

- Stable CHF (for four weeks).
- Left ventricular ejection fraction (EF) < 40% or,
- EF ≥ 40% with clinical symptoms of heart failure (preserved EF).
- Age between 20 and 85 years.

Exclusion criteria:

- Acute myocardial infarction within four weeks.
- Unstable angina pectoris.
- Serious rhythm disturbances.
- Symptomatic peripheral vascular disease.
- Obstructive pulmonary disease with forced expiratory vital capacity > 50% of predicted.
- 6MWT > 550 m, and workload on the cycle ergometer test >110 W.
- Known significant comorbidity that would prevent entry into the study due to known terminal disease or inability to exercise (e.g. severe musculoskeletal disorder, advanced valvular disease).
- Long-term care establishment.

The study was approved by the Regional Committee for Medical Research Ehtics and by the Norwegian Data Inspectorate. All patients gave their written informed consent to participate after receiving verbal and written information.

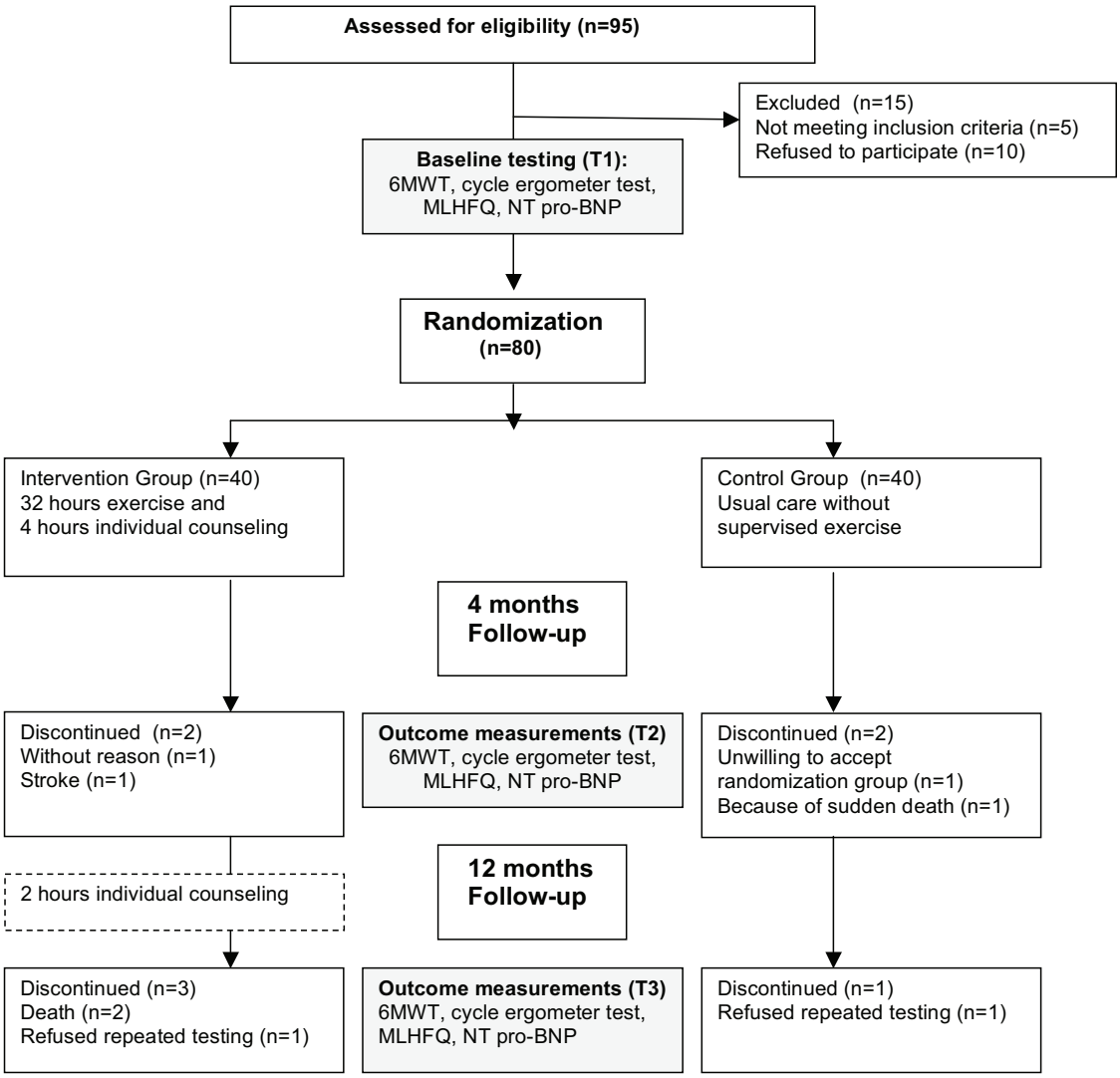

Figure 1. Flowchart

The Norwegian Ullevaal model

The Norwegian Ullevaal model consist of a group-based exercise training program including simple aerobic dance movements. The exercise training program is guided with music and includes endurance, strength, flexibility and stretching exercises in addition to group-based and individual counseling (Paper I). It is an interval training program with three intervals of high intensity (15-18 on Borg scale [63]). The total duration of the exercise training part is 50 minutes (Figure 2).

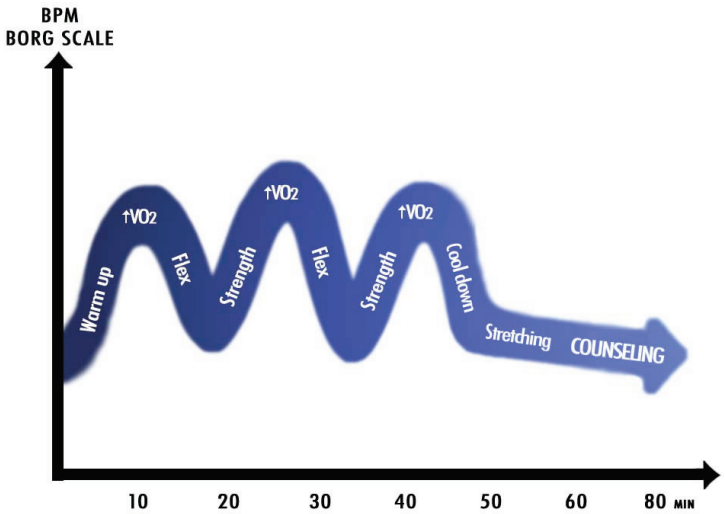

Figure 2. A schematic illustration of the group-based aerobic interval-training program. The duration is 50 minutes of exercise plus 15 to 30 minutes of counseling. The figure shows three peaks of high intensity (↑VO_2). The intensity is adjusted using the Borg Scale and beats per minute (BPM) of the music pace. Coordination exercises were included throughout the program.
VO_2 = oxygen consumption, Flex= flexibility exercises.

The group-based counseling part lasted from 15-30 minutes, depending on the patients' needs. The program was offered twice a week for a total of 32 exercise sessions. Patients had up to six months to complete the 36 sessions before the post exercise test (T2) took place. In addition the patients were offered four individual counseling visits with a CHF nurse, during the exercise training part in addition to two counseling visits during the follow-up (12 months).

The aim of the exercise training intensity was to achieve a heart rate (HR) of 90-95 % of the maximum HR (HR_{max}) achieved on the cycle ergometer test at baseline. A typical HR curve during an exercise training session is shown in Figure 3.

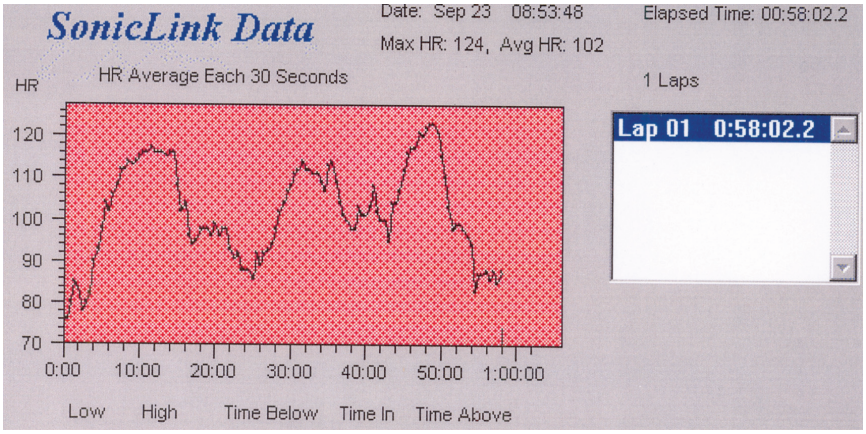

Figure 3. Example of a patient heart rate (HR) during one exercise training session. This patients HR_{max} was 129 beats/min during the cycle ergometer test at baseline. HR_{max} during the exercise training session was 124 beats/min (96% of achieved max). Average heart rate was 102 beat/min (79% of achieved HR_{max}).

A detailed description of the Norwegian Ullevaal model is presented in Paper I, including appendixes of exercises (Paper I, Appendix 1.) and music pace (Paper I, Appendix 2. and 3.).

Outcome measurements

All measurements were obtained at baseline (T1) and repeated after intervention (mean 22 ± 3.8 weeks) (T2) and after the12 month follow-up (mean 54.3 ± 2.8 weeks) (T3). The statistical analyses are described in the respective Papers (II, III, IV) and will only briefly be mentioned here.

Six minute walk test

Functional capacity was assessed as the distance walked during a 6MWT [64]. The 6MWT was performed in a 125 m pre-marked hospital corridor. The patients were instructed to walk from end to end at their own pace, attempting to cover as long distance as possible within six minutes. Stops and rests were allowed, if needed, and standard encouragements were used after three minutes ("you are doing well, and you have three minutes left"). The first 6MWT was performed at screening to select the right population (6MWT ≤ 550 m) and to familiarize the patients with the procedure. A second 6MWT was performed at baseline. A physical therapist (B.B.N.), or one of the three study nurses performed all screening and baseline tests. Three other physical therapists and three other nurses who were blinded to the clinical data and group assignment of the patients carried out all the follow-up tests. The 6MWT has demonstrated an ability to provide valid and reliable [65] information of functional capacity for patients with CHF [66].

Cycle ergometer test

The patients maximal exercise time and workload were evaluated on an electrically braked cycle ergometer (Ergometrics 800, Ergoline, Bitz, Germany). The work was

performed in the sitting position and a 12 lead ECG was recorded continuously during exercise, and for five minutes after work. We used a test protocol with an initial load of 30 W lasting for one minute, whereupon the load was increased step-wise by 10 W/min until exhaustion or a reported perceived exertion (RPE) on the Borg scale [63] of 17-18 [67]. Heart rate (HR) was measured from the ECG, and auscultatory systolic blood pressure was measured on the right arm every third minute. The total exercise time in seconds and the maximal work load the patients maintained for 60 seconds were recorded. For patients with CHF, stage increments of 10 to 15 watt every minute during the cycle ergometer test have been recommended [68].

Health related quality of life

HRQL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [69]. In clinical trials and clinical practice, the MLHFQ is the most frequently used disease-specific measure of HRQL in studies with CHF patients [4,70]. The questionnaire is a 21-question self-assessment questionnaire with a maximum score of 105. The higher the score the lower the HRQL. The MLHFQ has been shown to be a valid [69] and reliable [69,71] disease-specific measure of HRQL in patients with CHF.

Blood samples

Venous blood samples were taken at rest between 8 and 9 am, in a sitting position, after overnight fasting (before intake of medication) and measured with standard procedures at UUH, Oslo, Norway. NT pro-BNP was measured in EDTA-plasma with the Elecsys proBNP sandwich immunoassay on Elecsys 2010 (Roch Diagnostics). The inter-assay

coefficient of variation in our laboratory was 7 %. NT pro-BNP samples were stored at -80°C until analyses were performed.

Sample size calculation and statistical analysis

A clinically important effect of exercise training was estimated to be a difference between groups of 50 meters on the 6MWT from baseline to post exercise test. With a significance level (Type I error or α) of 5%, a Type II error or β of 20%, which indicates a statistical power of (1- β) 80%, and an estimated SD of the 6MWT of 90 m, it was calculated that 37 patients were needed in each group. To allow for some drop-outs, it was decided to include a total of 80 patients. In Paper II and Paper III, data were analyzed and presented according to intent to treat (ITT) principle. The statistical methods used are presented specifically in each paper. The effect sizes (Paper II and III) were interpreted according to Cohen`s index [72], where 0.2 refers to a small change, 0.5 to a moderate change and 0.8 and above to a large change.

SUMMARY OF RESULTS

Paper I

This Paper described the background, the mode and the intensity of the Norwegian Ullevaal model, which was developed at and clinically used for patients with CAD for three decades, at UUH. The Norwegian Ullevaal model is used as intervention in Paper II, III and IV. Paper I is written as a case report, with four male patients with CHF in NYHA class III who were randomly selected from the intervention group in the study population.

The patients increased their 6MWT distance with 117, 66, 135 and 143 m, respectively. Patient 1,2, and 3 increased their time on the cycle ergometer test with 17, 25 and 52 %, respectively. Patient 4 did not complete the cycle ergometer test due to his pacemaker. The patients increased their MLHFQ with 42, 8, 18, 53 points, respectively. There were no complications related to the exercise training and no adverse events.

Paper II

This Paper presented the main results of functional capacity and HRQL measurements in the intervention group and the control group before and after the four months (22± 3.8 weeks) intervention period (from T1 to T2). A total of 80 patients were included in the study.

There were no complications of any kind during exercise testing or the exercise training. The average compliance (actually performed exercise training sessions divided by possible sessions) in the intervention group was 95%. Only one patient did not give

any reason for drop-out. There were no significant differences between groups regarding patients' baseline characteristics, with a mean age of 70 ± 8 years and an EF of 30.2 ± 7.6 %. There were no significant differences between groups in functional capacity at baseline, but the MLHFQ score was significantly higher (worse) in the intervention group compared to the control group. After the intervention (mean 22± 3.8 weeks), functional capacity improved significantly in the intervention group compared to the control group for all measurements (6MWT; +58 m versus -14 m., $p< 0.001$, cycle ergometer test; +10 W versus -1 W, $p< 0.001$ and, 57 sec versus -8 sec, $p< 0.001$). HRQL improved significantly in the intervention group compared to the control group ($p=0.03$), and a significant inverse correlation was found between delta MLHFQ and delta 6MWT ($r=-0.49$, $p<0.05$).

Paper III

This Paper presented the long-term results of the Norwegian Ullevaal model on functional capacity and HRQL assessments (same population as Paper II). After 12 months (mean 54.3 ± 2.8 weeks) the improvements were still significant for all the outcome measurements in the intervention group compared to the control group. (6MWT; 41 m versus -20 m, $p<0.001$, work load; +10 W versus -1 W, $p=0.001$, exercise time; 53 sec versus -6 sec, $p=0.003$, and MLHFQ; 10 points improved versus 6 points worse, $p=0.003$).

Paper IV

This Paper summarized the changes in NT pro-BNP over time (same population as Paper II and III). Available blood samples at baseline were 78, at T2; 70, and at T3; 69. There were no significant changes in NT pro-BNP levels between groups from baseline to either T2 or T3. No significant correlation between change in NT pro-BNP and change in functional capacity (6MWT; $r=0.12$, $p=0.33$, Exercise time; $r=0.04$, $p=0.72$) was observed in the whole study population.

There was a significant inverse correlation between NT pro-BNP and 6MWT ($r= -0.24$, $p=0.035$) and between NT pro-BNP and exercise time ($r=-0.48$, $p< 0.001$) at baseline.

GENERAL DISCUSSION

Subjects

A total of 80 patients participated in this study. The subjects included in the study need to be a representative selection of the population of patients with CHF in order to generalize the results from this single trial to a larger population [73]. All patients in the present study were informed that they had to be willing to exercise twice a week for four months if allocated to the intervention group, even though we did not know, before completing the study, what the effect of the Norwegian Ullevaal model would be. All patients admitted to the heart failure out-patient clinic were screened for inclusion in the study, but we did not register the patients who did not satisfy the inclusion criteria. Some patients where excluded due to walking aids. Most of the patients were excluded due to a walking distance of above 550 meters during the 6MWT. The results of the present study are therefore valid for a population of patients with CHF in NYHA- class II-IIIB, who are between 45 and 85 years, who walk without the use of walking aids and who walk a distance during the 6MWT of < 550 meters.

The prevalence of CHF increases with age, but the majority of patients included in previous studies of an exercise training intervention, was of a younger age than our population [39,42,52,74-76]. During the last decade, pharmacological therapy of CHF has involved the use of beta-blockers. However, data are limited regarding exercise training intervention in patients with CHF who are on optimal medical treatment. In our study, all patients were on optimal medical treatment and more than 90 % were treated with beta-blockers.

Design

The randomized controlled trial is considered the gold standard design when assessing the effect of treatments (Paper II, III, IV) [73]. Random allocation, cover of allocation, blinding and the lack of patients´ attrition to the intervention protocol are considered the most important methodological factors to ensure a high internal validity. It is not possible to blind patients to an exercise training intervention, but the follow-up tests (T2 and T3) were assessed by blinded test persons and the patients were told not to reveal to which groups they belonged at follow-ups. Case reports (Paper I), describe various aspects of clinical practice but do not test hypotheses, establish cause-and-effect relationships, or prove effectiveness [77]. A Case report design for Paper I was chosen to be able to thoroughly describe and discuss the Norwegian Ullevaal model, an interdisciplinary, group-based program that have never previously been described in the literature.

The Norwegian Ullevaal model

Group-based and interdisciplinary program

Most exercise training studies have included individual based or home-based exercise training programs for patients with CHF. During the three last decades we have acquired substantial knowledge and extensive experience with the Norwegian Ullevaal model used as an exercise training program for patients with cardiac disease at UUH. There existed a need, therefore, to first describe our program (Paper I), and secondary to evaluate (Paper II, III and IV) our program in respect to the feasibility of its use, and its short and long-term effects on patients with CHF.

The literature has described the advantage of using a group-based exercise training program [78-80]. The individuals experience and sense of belonging, feeling supported and learning from each other are beneficial. All these factors seem to be of importance regarding enhance commitment [79]. Positive feedback, perception of success, and expectation of success are important for compliance and adherence to an exercise training program [61]. The Norwegian Ullevaal model benefits from the interactive and social components described by Bandura`s social learning theory, but the program requires the skills and knowledge of a professional instructor (physical therapist) to conduct the exercise training [81]. Another advantage of a group-based exercise training program is that it is not expensive and does not require any sophisticated equipment. However, there is a need for additional studies to evaluate the cost-benefit effects of a group-based program compared to other programs. Since this program was performed in an out-patient clinic, it might be thought of as a useful "beginner"- program to prepare patients with CHF to exercise on their own.

The use of an interdisciplinary program makes it difficult to separate the effect of the group-based exercise training and counseling from the individual counseling with the nurse. This study examined the effect of the whole program, and we are not able to say which aspect is the most significant. But, patients with CHF usually have several comorbidities and polypharmacy, and are probably most likely to benefit from such an interdisciplinary program, including individual counseling.

Intensity

Exercise training intensity can be expressed as a percentage of HR or maximal oxygen uptake (VO_{2max}) or rate of perceived exertion (RPE) [82] (Table 2). The term peak oxygen uptake (VO_{2peak}) is the highest rate of oxygen consumption measured during the exercise test, regardless of whether or not a VO_2 plateau was reached. VO_{2peak} is more commonly used in patients with CHF due to inability to achieve the VO_{2max} criteria [83].

Table 2. Classification of intensity during physical activity.
Adapted from American College of Sport Medicine [82].

Relative intensity/ Perception of effort	HR_{max} %	VO_{2max} %	RPE
Very light	< 35	< 20	< 10
Light	35-54	20-39	10-11
Moderate	55-69	40-59	12-13
Hard	70-89	60-84	14-16
Very hard	≥ 90	≥ 85	17-19
Maximal	100	100	20

HR_{max}= maximal heart rate, VO_{2max} = maximal oxygen consumption, RPE=Rate of perceived exertion (Borg scale 6-20 [63]).

There is no consensus on exercise training intensity for patients with CHF because the great variation displayed by the studies prevents the formation of a basis upon which recommendations could be built. The latest recommendations for exercise training in CHF patients from the ESC working group (2001) state that patients with CHF should exercise at moderate to high intensity (40-80% of VO_{2peak}) [68]. In the latest statements

from American Heart Association Committee on exercise, rehabilitation, and prevention (2003) it is reported that the most frequently used exercise training intensity range from 70% to 80% of $VO_{2peak.}$ Furthermore, they stated, based on one article [84], that exercise training intensity during interval training did not seem to influence the magnitude of the increase in functional capacity [2].

In contrast, high-intensity aerobic interval training is reported to be, in recent studies, twice as effective as low-moderate exercise training with respect to improving VO_{2peak} in patients with CAD [55], patients with CHF [45] and in healthy subjects [54]. When the total volume of exercise training is held constant, more vigorous exercise training seems to provide greater health benefits than moderate exercise training [85]. Aerobic interval training allows patients with compensated CHF to complete short, but high intensity, exercise training periods that would not be possible with a continuous exercise training program [86,87]. In our exercise training program the average intensity was between 70-80 % of the HR_{max} at baseline (Figure 2). Thus the total cardiac work was not necessarily higher than in continuous exercise training programs, even though the intensity was high (90-95% of the HR_{max}) during the three interval-peaks.

Outcome measurements

Functional capacity - 6MWT and cycle ergometer test

The 6MWT has been used as an end-point for examining functional capacity in several clinical trials in patients with CHF [88]. It is a well tolerated and an inexpensive alternative method to evaluate functional capacity and probably more representative of the

individuals capacity during daily activities, compared to maximal exercise testing methods [66,89,90].

Testing of submaximal exercise using the 6MWT appears to be a more sensitive indicator of a training effect than maximal cardiopulmonary exercise tests [89]. In addition, the walking distance assessed by the 6MWT has been shown to be significantly related to VO_{2peak} ($p<0.001$) [91,92], and to represent an independent predictor of mortality and morbidity in patients with CHF [93,94].

The patients in our study had a mean walking distance during the 6MWT of 456 meters at baseline. This is in accordance to some other studies [89-91], but in most studies that have included the 6MWT as an endpoint, the patients have covered a much shorter walking distance at baseline (mean 266-385 m) [27,49,95-98]. The 6MWT in healthy, age matched subjects range from 400-700 m [99]. However, the walking distance varies by up to 30% between the few published studies [99]. One explanation for the high walking distance during the 6MWT in our population could be that the Norwegian population is familiar with physical activity and seems to have a high fitness level [89] compared to other populations from other countries. In addition, differences in the length of the hallway used during the 6MWT, resulting in more or less turns, may also affect the covered walking distance during the 6MWT.

VO_{2peak} is considered to be the gold standard for evaluating functional capacity in patients with CHF [100]. We did not have the equipment or personnel to perform this test at the Department of Cardiology at the moment we designed the present study. However, the improvement in the 6MWT in the intervention group was in our study complemented by the significant improvements in workload and exercise time during the cycle

ergometer test. The patients performed the cycle ergometer test using a stepwise increase in workload (10 W/min) until volitional exhaustion was reached (Borg scale 17-18). A protocol of equal amount each minute is suitable for patients with CHF [101] and has been used at our hospital over the last decades. Functional capacity measurements (VO_{2peak}, maximal cycle work rate and 6MWT) have shown to correlate significantly with one another. Maximal cycle work rate has shown to correlate significantly with VO_{2peak} (r=0.85) in a study with a similar baseline walking distance during the 6MWT (448 m) and using the same cycle ergometer protocol as in our study[102].

Health related quality of life

HRQL is a widely used outcome measure in randomized controlled trials of exercise intervention, and a number of disease-specific questionnaires for CHF have been developed [70]. There are mainly two different types of HRQL measurements used in studies with CHF patients: generic and disease-specific questionnaires. Generic questionnaires aim to provide a summary of HRQL, irrespective of the disease or the condition of the patient. Disease-specific questionnaires focus on the difficulty experienced by the specific patient group or by individuals in specific disease states [103]. In Paper I, II and III, HRQL was evaluated with the disease-specific questionnaire, MLHFQ. Considering its widespread use in exercise intervention studies [104], the MLHFQ was the clear choice. At our hospital we have extensive experience with the MLHFQ, due to its simplicity, and the fact that it is easily understood for older patients. The MLHFQ is a valid and reliable measurement of HRQL in patients with CHF [69]. Similar to results

from the EXERT trial [60], the patients in our study had a relatively low score of the MLHFQ (mean 27.5) compare to other studies on patients with CHF [53,96,105].

N-terminal pro B-type natriuretic peptide

Neurohormonal activation is a hallmark of CHF [106]. In recent years there have been several studies which have focused on the clinical usefulness of circulating markers in patients with CHF [7,107]. There may be some advantage in NT pro-BNP measurements compared to BNP, mainly because plasma BNP is relatively more labile than NT pro-BNP [108]. BNP analysis is sensitive to temperature change and is also affected by the type of tube that blood is collected in. This is in contrast to NT pro-BNP who is not subject to those types of measurement errors [18].

Statistics

In the present study, ANCOVA was used to assess end points between groups from baseline to follow-up measurements (Paper II, III and IV). ANCOVA adjusts for possible baseline differences and is considered a more powerful analysis than alternative methods like Student *t*-tests and ANOVA [109,110]. The main statistical limitation of the study is the relative low statistical power in Paper IV.

ITT analysis was used in Paper II and III. The primary analysis of a randomized controlled trial should always include ITT analysis, since it avoids the possibility of any bias associated with lost to follow-up or because of non-adherence of patients in the study. ITT with last value carried forward was used in case of missing values. Conducted both by per protocol analysis and by ITT, these analyses resulted in similar values.

Results

The main findings in this study demonstrated that patients with CHF in NYHA-class II-IIIB significantly improved their functional capacity and HRQL (Paper II and III) by participating in the Norwegian Ullevaal model compared to a control group. In addition, the improvements were still significant after 12 months. Despite randomization, the baseline scores regarding HRQL were worse in the intervention group. This was taken into consideration by including ANCOVA analysis when conducting comparisons between group differences of follow-up measurements (T2 and T3).

The compliance with the exercise training (actually performed exercise training sessions divided by possible sessions) in the present study was high (95%). High compliance was probably achieved due to; the opportunity to extend the total number of exercise training periods to 24 weeks; the opportunity of meeting other patients with the same kind of problems; the individual counseling with the CHF nurse; the physical therapists ability to make exercise safe and motivating and the collegiality that developed among patients and the encouragements and support they provided to each other. The non-existence of complications or any cardiac events during the exercise training may be seen as evidence of the safety of the program.

Why is this the first study to document sustained effects of exercise training in patients with CHF?

It is well known that the favorable adaptations obtained after prolonged exercise training disappear rapidly when a person stops exercising [111]. Several studies of the physiological

variables with different duration of detraining confirms this observation in athletes [112], as well as in patients with CAD [113,114] and patients with CHF [115]. We have no data on physical activities between the post intervention test (T2) and the 12 month follow-up (T3) (exercise adherence data). Nevertheless, a significant difference between the groups at the 12 month follow-up (with no significant loss of functional capacity) indicated that the patients in the intervention group had been more physically active than the control group.

Adherence to an exercise training program depends almost entirely on the patients motivation [116]. The main objective for the physical therapist (instructor) is to make the program motivating and meet the individual's needs. An important factor when counseling patients in exercise training is the skill and knowledge of the physical therapist to transfer feeling of safety and joy about exercise training [29,117]. The main reason for drop-outs from exercise training programs is the monotony of the exercise training regime [116]. With a skilful physical therapist as instructor for the exercise training, the Norwegian Ullevaal model will never be monotone. Informal comments from the patients in the intervention group indicated that they found it enjoyable and motivating to exercise with music and varied intensity. Informal comments indicate that the high intensity exercises in this program could lead patients to dare to continue exercise training on their own. In addition, some patients continued a group-based exercise program in their home districts. Their family also found it safe to accompany relatives with CHF on a brisk walk because they had been informed of the high intensity aspect of the exercise training program. This observation stands in contrast to studies that evaluate

exercise training and find that high-intensity is associated with a lower adherence to exercise training than a lower-intensity [118,119].

Table 3 summarizes interventions and results of randomized controlled trials with follow-up ≥ 10 months. To our knowledge, the present study is the only study that showed improved long-term effects of exercise training on functional capacity and quality of life in patients with CHF. Exercise adherence rates decrease as trial duration increase [61]. Two studies followed the patients for six [75] and five [120] years. These two studies could not be compared to the others [60,74,95,121,122]. All the studies (in Table 3) included interventions at a lower exercise training intensity compared to the program of high-intensity in our study. Most of the studies offered a rather monotone exercise training program with either walking or ergometer cycle. Our results suggest that the intensity of the exercise training in the Norwegian Ullevaal model may be an important factor for the improved functional capacity and HRQL and also the long-term effect. Another important consideration is the selection of activities that the patients enjoy. All these factors may be significant for the prolonged effect of the Norwegian Ullevaal model.

Table 3. Randomized controlled trials on the long-term effect (>10 months) of exercise intervention programs in patients with CHF

	N	Mean age	NYHA	Intervention	Follow-up	Endpoints	Diff between groups
Augustin et al[120] 2008	57 exercise 55 control	75	II-III	Group-based, coordinated by a nurse 2/week for 8 weeks + 1/week for 16 weeks by an exercise instructor	5 years	NYHA 6MWT HRQL Hosp.	ns ns ns ns
Nilsson et al [122] 2008	40 exercise 40 control	70	II-III	Group-based, high-intensity (Borg: 15-18), interval training 2/weeks for 16 weeks	12 months	6MWT Exercise time HRQL	61 m 59 sec 16 points
Dracup et al [74] 2007	87 exercise 86 control	54	II-IV	Home-based 4/week (walking) + monthly visit. 40-60% of HR_{max} + resistance training; 80% of 1RM	12 months	All-cause hosp 6MWT VO_{2peak} HRQL Multiple hosp.	ns ns ns ns 12.8% vs 26.6%
Mueller et al [75] 2007	14 exercise 13 control	55		Ergometer cycle (Borg: 12-14) 5/week, 30 min + out-door walking 2/day (4 weeks)	6 years	VO_{2peak} Mortality	ns ns
Witham et al [95] 2007	23 exercise 19 control	80	II-III	Seated exercises 2/week, 12 weeks + weekly phone contact with physical therapist during follow-up	19 months	6MWT HRQL Mortality	ns ns ns
EXERT [60] 2002	64 exercise 75 control	65	I-III	Cycle, treadmill and arm ergometer, 60-70 % of HR_{max} + resistance (40-60 of 1RM), 2/week for 3 months + provided cycle and free weights for home-base exercise training	12 months	6MWT HRQL VO_{2peak}	ns ns ns
Willenheimer et al [121], 2001	17 exercise 20 control	64	II-III	Cycle ergometer, interval, 80% of VO_{2peak}, 15 min 2/week increased to 45 min, 3/week, totally 16 weeks	10 months	VO_{2peak} HRQL	ns ns

NYHA = New York Heart Association, 6MWT= six minute walk test, HRQL= health related quality of life, Hosp = hospitalization, ns = not significant, IRM= one repeated maximum

Our data did not support the notion that neurohormonal status would improve as a result of exercise training in stable patients with CHF (Paper IV). This observation is in line with a recently published observational study [27], but stands in contrast to previous studies [24,25,123]. However, we found a significant correlation between NT pro-BNP and functional capacity at baseline, in line with previous reports [7,24,27].

In recent years, several studies have studied the relationship between improvement in functional capacity and change in levels of NT pro-BNP [24,25,123] or BNP [26,28,124]. The studies differ largely in design, duration and mode of exercise training, as well as in the outcome variable as measure of neurohormonal burden, BNP and NT pro-BNP. Exercise training in patients with CHF has been shown to primarily affect peripheral working muscles [125,126], which may not cause an effect on the NT pro-BNP levels. Our study population was on optimal medical treatment and the levels of NT pro-BNP in the present study were relatively low (median 188 pmol/l) compared to other studies [24,25,123], and reduced levels would possibly be difficult to obtain.

CONCLUSIONS

- The Norwegian Ullevaal model is feasible and improves functional capacity and quality of life in patients with CHF, both in the short and the long-term.

- The Norwegian Ullevaal model is safe and there is no need for costly equipment for monitoring patients. In addition, the program can be performed with a high compliance rate in patients with CHF.

- The Norwegian Ullevaal model does not support improvement in neurohormonal status, as no significant reduction in plasma levels of NT pro-BNP was observed.

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