Title page: Protocol study

“Eccentric muscle training in cardiac rehabilitation: randomized controlled trial to evaluate effectiveness and feasibility in heart failure patients with reduced ejection fraction”

Antwerp University Hospital

Drie Eikenstraat 655,

2650 Edegem

Belgium

Contact: xxx

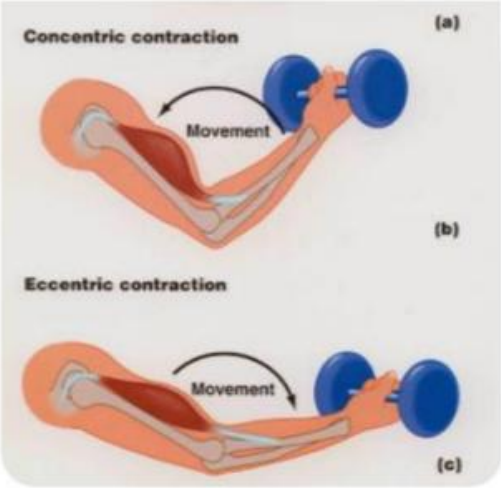
Introduction

In chronic heart failure patients (CHF), a wide range of drugs significantly lower morbidity and mortality. Despite pharmacological interventions, reduced exercise tolerance with fatigue and dyspnea at exertion persist. Sarcopenia, which means loss of muscle mass and function, leads to poor exercise capacity and quality of life in CHF and is an independent predictor of death [1]. Besides the fact that sarcopenia is limiting the exercise capacity, cardiac limitations lead to the impossibility to overload the muscles during endurance training in this patient population. Overloading of the skeletal muscles is crucial to achieve training responses that result in higher exercise tolerance. There is a need to identify adjunct exercise training strategies that overload the skeletal muscle in a manner that is efficient and feasible in CHF.

Eccentric muscle actions (=whereby muscle lengthens while producing force) has recently been proposed as a potentially effective exercise training strategy for patients with exercise intolerance [2-4]. The rationale relates to the finding that eccentric exercise results in gains in muscle power with a lower metabolic and cardiorespiratory demand than conventional exercise training [2-4]. Moreover, muscles are capable of achieving higher absolute forces during the eccentric phase resulting in higher training load and hereby training volume.

Eccentric muscle activity can be obtained by:

1. <u>Eccentric overload training</u>
   Traditionally, resistance training is performed using the same external load in the concentric and the eccentric phase of the range of motion.



<u>Figure</u>: The best example of both concentric and eccentric contractions is the biceps curl when holding a dumbbell of 1kg in the hand. When the arm is curled up toward the shoulder, the M. Biceps Brachii contracts. Only when the force delivered by the muscle is greater than the weight of the forearm and dumbbell, the hand goes towards the shoulder. This is called a concentric movement because the muscle shortens. When the hand is lowered back toward the starting position, the M. Biceps Brachii controls the weight of the forearm and dumbbell. This is called an eccentric movement because the M. Biceps Brachii gets longer.

   Eccentric overload training can be performed on specialized muscle training devices in which the muscle is being overloaded during the eccentric phase of the exercise. This means that during the time span of one range of motion, a higher load is used in eccentric overload training in comparison with traditional strength training.

2. <u>Eccentric cycle training on a bike ergometer</u>
   The bike pedals are driven in a backward direction by an electric motor and the subject has to maintain a backward pedaling rate by exerting a given force against the pedals. Since this

way of cycle training knows a lower metabolic and cardiorespiratory demand, a higher workload (by 4 to 5-fold) in comparison with conventional cycle training can be reached.

The *dose-response relationship* between training load and benefit describes that the increases in muscle strength and muscle mass is proportional to the magnitude of force developed. The higher the training load, the higher the benefit will be in healthy adults and elderly [5,6]. However, eccentric overload training has not been studied in heart failure patients.

Study aim:
*Primary objective: To assess the training effects regarding exercise capacity (VO2 peak), muscle strength and muscle mass in rehabilitation of CHF in which training volume is optimized by

1. Eccentric overload training: a higher load is used in comparison with traditional strength training
2. Eccentric cycle training: a higher load is used in comparison with traditional cycle training with low cardiorespiratory and metabolic demands

*Secondary objective: The safety and feasibility of eccentric overload training in HF will be evaluated based on the adverse events reported in a case report form.

Hypothesis:
It is hypothesized *that greater muscle strength* and *muscle mass* are obtained by eccentric muscle training in comparison with conventional training because *higher training volumes* can be used. It is hypothesized that better outcome regarding muscle function and mass will influence *VO2 peak* and *physical activity level* in this patient population.

PICO

Patients

40 CHF patients will be included in this study.

The amount of 40 patients is chosen because this seems a reasonable and reachable amount over the time frame of 2 years. The main goal of this study is to describe feasibility of eccentric training in patients with chronic heart failure and to compare its outcome with the mean outcome of usual care. (control = usual care which is concentric training).
This is in line with the study of Besson et al. in which eccentric training is compared with concentric training in 30 patients with heart failure. [7].

Inclusion criteria:

-HFrEF patients with ejection fraction <40%
-New York Heart Association (NYHA) functional class II–IV
-Referred for participation in the regular 13-week exercise based rehabilitation program.
-Exercise intolerance (<85% of predicted VO2 peak)
-clinically stable for > 6 weeks, optimal medical treatment for > 6 weeks

Exclusion criteria:

-Contra indications for cardiac exercise rehabilitation as per consensus guidelines and recommendations
-Musculoskeletal disorders that hamper (progression in) strength training
-Non-stabilized acute coronary syndrome

-Current acute heart failure
-Patient having sustained a recent (<3 months) procedure that could act as a confounder to increase VO2peak (i.e., coronary artery bypass graft surgery, percutaneous coronary intervention, cardiac resynchronization therapy, valve surgery or reparation)

Intervention

Intervention and Control group:
Patients that are referred for exercise-based cardiac rehabilitation will be randomized 1:1 to an Intervention Group or Control Group.

Usual Care in both groups:
Patients will perform supervised cardiac rehabilitation 3 times/week during the intervention period of 13 weeks.

- Endurance training will take place following a fixed protocol. This will be 20 minutes aerobic treadmill training with a target heart rate corresponding to 90% of the 2nd ventilatory threshold measured at the baseline Cardio Pulmonary Exercise Test (CPET) and with rate of perceived exertion (RPE) 12-15/20.
  After five weeks of training, a new CPET will be performed and training intensity will be redefined to build in progression.
- Strength training and muscular strength testing will take place on four Technogym Biostrength training machines: the supine leg press, chest press, vertical traction and seated row. Each exercise will be performed 3*10 times with clear instructions to avoid the valsalva maneuver during strength training. One Repetition maximum (1RM) will be tested at baseline. In the concentric phase strength training, an external load of 40-70% of 1RM will be used. After five weeks of training, a new 1RM strength test will be performed and external load will be redefined to build in progression.

Intervention group:
Eccentric training will be added to Usual Care
1. Eccentric overload training: during the Range of Motion of a traditional (concentric) strength exercise, the eccentric phase will be overloaded (+10-20%) with RPE 12-15/20. This would not take extra time.
2. Eccentric bike training: 5-15 minutes eccentric bike training with cycling load = 50-80% of the Wattmax during the CPET with RPE 12-15/20.

Control group:
As alternative for eccentric bike training, there will be 5-15 minutes of concentric bike training added to the standard program (intensity = 90% of the 2nd ventilatory threshold) with RPE 12-15/20.

Cardiac work-up

Cardiac work-up will be performed at the CR service and is part of daily practice during a rehabilitation trajectory.
Goal of this work-up is to assess general comorbidities, risk factors for cardiovascular diseases and exclusion criteria to the partially remote cardiac rehabilitation intervention.
This work-up consists of:

- Non-fasting blood sample: Blood parameters regarding cardiovascular health or muscle function: hematocrit, hemoglobin test, creatinine, CKD-EPI, CRP, CK, HDL, LDL, triglycerides, ferritin.
- Resting ECG
- Spirometry: forced expiration technique measurement of FEV1, FVC
- CPET
    - VO2 peak
    - Slope VE/VCO2
    - Other CPET derived parameters: Wattpeak, HRmax, chronotropy, ventilatory threshold 1 (VT1), ventilatory threshold 2 (VT2), VO2/HR, PETCO2, Exercise oscillatory ventilation, VO2/W
    - ECG changes
    - blood pressure

Outcomes

Data will be analyzed in a pseudonymized manner. Since all patients are included in the standard rehabilitation patient trajectory, standard parameters regarding evolution and medical follow up is saved in the EPD.

1. PRIMARY OUTCOMES

Muscular strength (1 RM) measured with Technogym Biostrength training devices, isokinetic-concentric-eccentric knee extensor force (Biodex measurement), handgrip strength analysis

2. SECONDARY OUTCOMES

a. Exercise capacity (VO2 peak) measured with a maximal cardiopulmonary exercise test (CPET) on a bicycle following guidelines [9,10].

b. Changes regarding body composition (muscle mass, percentage of body fat) measured by bioelectrical impedance analysis.

c. The safety and feasibility of eccentric overload training in HFrEF will be evaluated based on the adverse events reported in a case report form.

d. a questionnaire will be used to have insight in Quality of Life: EQ5D-5L

c. Blood parameters regarding cardiovascular health or muscle function = standard of care within cardiac rehabilitation

➔ Statistical plan

A T test will be used to look at the evolution of main outcome after the intervention.
When data are normally distributed, 2 way anova test will be used to compare the mean of outcome of the eccentric training group with the usual care group. Mixed models analysis will be done and interfering factors will be defined.

➔ Data Management

Data will be stored for 20 years, and will be available at the cardiac rehabilitation unit. Redcap will be used for data management.

Additional information

Addendum CPET

Cpets will be performed following guidelines regarding cardiopulmonary exercise testing.
Following bicycle RAMP protocols will be used:

- RAMP 5W/min
- RAMP 7W/MIN
- RAMP 10W/min
- RAMP 15W/min
- RAMP 20W/min
- RAMP 25W/min
- RAMP 30W/min
- RAMP 35W/min
- RAMP 40W/min

The RAMP protocol will be chosen based on prediction of the VO2 peak (=equations of the FRIEND study). (6)

Addendum Questionnaire

The survey will be filled in using the online Qualtrics software program.
Patients will fill in the survey on a tablet on the same day of the start of the rehabilitation program.
All questions are translated in Dutch (validated form).

Following questions are part of the survey:

a. <u>EQ5d 5L</u>

Figure 1 / UK (English) EQ-5D-5L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

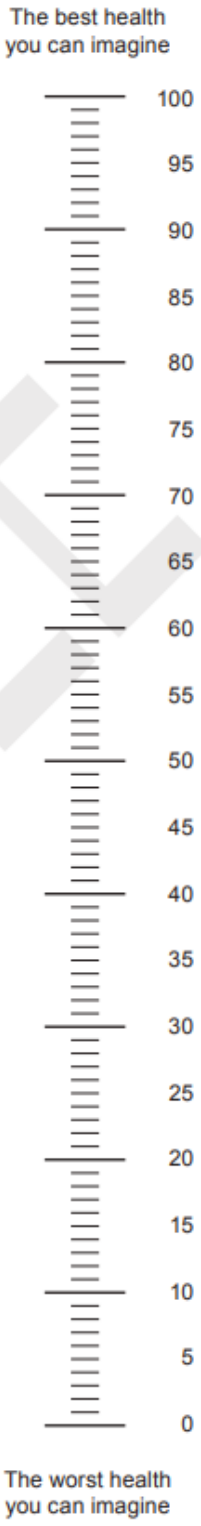
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



References

1. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC); Antonio Pelliccia et al.; European Heart Journal (2021) 42, 1796
2. Cardiac rehabilitation: clinical effectiveness and utilisation in Belgium.; Ilse Van Vlaenderen et al; KCE Reports 2010; 140C. D/2010/10.2738/67.
3. 'DNA' may not mean 'did not participate': a qualitative study of reasons for non-adherence at home- and centre-based cardiac rehabilitation; Miren Jones et al.; Family Practice, Volume 24, Issue 4, 2007
4. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data; Lis Neubeck et al.; Eur J Prev Cardiol. 2012 Jun
5. ATS/ACCP Statement on cardiopulmonary exercise testing; American Thoracic Society; American College of Chest Physicians; Am J Respir Crit Care Med. 2003 Jan 15;167(2):211-77
6. Prognostic comparison of the FRIEND and Wasserman/Hansen peak VO2 equations applied to a submaximal walking test in outpatients with cardiovascular disease; Chiaranda et al.; Eur J Prev Cardiol.2019 Aug 26
7. Eccentric training in chronic heart failure: Feasibility and functional effects. Results of a comparative study; Besson et al. ; Ann Phys Rehabil Med. 56 (2013)