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Effect of selected gene polymorphisms on the effectiveness of cardiac rehabilitation of patients with heart failure

Submission date
26/12/2024

Recruitment status
No longer recruiting

Registration date
12/01/2025

Overall study status
Ongoing

Last Edited
07/01/2025

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The aim of the study is to determine whether genetic variation [ACE (rs4340; D/I), TNF-α (rs1800629, -308G/A i rs1799964, C/T), eNOS (rs179983, 894G/T; rs2070744, -786T/C i powtórzenie tandemowe w eksonie 4: 4A/4B) i BNP (rs198389, 381T/C)] has an impact on exercise tolerance, quality of life, self-esteem and physical activity after cardiac rehabilitation combined with i) pharmacological treatment and ii) neuromuscular electrostimulation (NMES) and pharmacological treatment in patients with stable chronic heart failure (HFrEF).

Who can participate?
Patients (men and women aged 40 to 80 years) with HFrEF due to coronary artery disease, hypertension or idiopathic HF. Patients will be referred for inpatient cardiac rehabilitation at the following centres:
1. Cardiac Rehabilitation Unit of the Municipal Hospital No 4 in Gliwice
2. Cardiac Rehabilitation Unit of St Barbara's Specialist Hospital No 5 in Sosnowiec

What does the study involve?
After patients have qualified for the study and agreed to participate in the biomedical experiment, blood will be taken and analysed for the polymorphism of genes. Serum remaining after centrifugation will be used to determine biomarker concentrations. Each patient will be assessed exercise tolerance, left ventricular systolic and diastolic function, quality of life, physical activity and selected anthropometric parameters such as body weight, height, waist and hip circumference. At the same time, a medication review will be performed by a clinical pharmacy specialist for each patient who participates in the study.

In the following days, patients admitted to the Cardiac Rehabilitation Unit of the Specialist Hospital in Sosnowiec will undergo standard cardiac rehabilitation according to the requirements of the National Health Fund. Patients admitted to the Cardiac Rehabilitation Unit of the Municipal Hospital in Gliwice, on the other hand, will be randomly assigned to one of two groups:
• The first group (NMESCR) will consist of 50 patients who, in addition to their pharmacological

treatment and standard cardiac rehabilitation, will undergo neuromuscular electrostimulation (NMES) 5 times a week (Monday to Friday) for a period of 40 minutes under the supervision of a physiotherapist (15 sessions). NMES will be carried out using an electrostimulation kit. The following muscles will be covered by the NMES: quadriceps (20 minutes) and triceps (20 minutes) of both lower limbs. Electrodes will be applied to the proximal and distal ends of the muscle bellies. An alternating rectangular symmetrical current of 35 Hz will be used. The pulse duration will be 0.4 ms. During the pulse series, an incomplete tetanic contraction of 30-45% of the maximum muscle force will be induced. The duration of the pulse series ('contraction duration') will be 2 seconds and the duration of the interval between the pulse series ('diastole duration') will be 4 seconds.
• The second group (CR) will consist of 50 patients who will receive only cardiac rehabilitation, as required by the National Health Fund, as well as pharmacological treatment.

At the end of the 3-week period of inpatient cardiac rehabilitation, the following parameters will be assessed for each patient:
1. Exercise tolerance
2. Left ventricular systolic and diastolic function
3. Quality of life using questionnaires and self-reporting
4. Selected anthropometric parameters such as body weight, height, waist and hip circumference
In addition, blood will also be taken for the assessment of biomarker levels.

A follow-up visit is planned at the end of the study, i.e. 12-16 weeks after the end of the in-patient cardiac rehabilitation, during which the following will be analysed:
1. Quality of life using the same questionnaires and self-reporting
2. Physical activity using questionnaires
3. Simultaneously, a clinical pharmacy specialist will perform a medication review for each patient.

What are the possible benefits and risks of participating?
Expected therapeutic/cognitive benefits:
There are currently no studies evaluating the effect of the following gene polymorphisms: ACE (rs4340; D/I), TNF-α (rs1800629, -308G/A and rs1799964, -1031T/C), eNOS (rs1799983, 894G/T; rs2070744, -786T/C and a tandem repeat in exon 4: 4A/4B) and BNP (rs198389, -381T/C) on the effectiveness of cardiac rehabilitation combined with pharmacological treatment in patients with HFeEF. Therefore, the results obtained may contribute to the development of new recommendations for health training in patients with HFrEF based on individual adjustment of the physical training programme used in cardiac rehabilitation and the pharmacological treatment applied, depending on the polymorphism of the ACE, TNF-α, eNOS and BNP genes.

Consequences of adverse events:
No adverse events are anticipated, as blood samples will be taken (10 mL before, 5 mL after) as part of routine laboratory testing of patients in the rehabilitation units. The use of NMES, on the other hand, is a therapeutic procedure used in rehabilitation, although not in cardiac rehabilitation, to improve skeletal muscle function. Other interventions consist in interviewing the patient to complete the following questionnaires:
• Medication review,
• The questionnaires to assess quality of life,
• Beck Depression Scale for self-report,
• The questionnaire to assess physical activity

Where is the study run from?
Jerzy Kukuczka Academy of Physical Education in Katowice

When is the study starting and how long is it expected to run for?
June 2024 to May 2026

Who is funding the study?
Jerzy Kukuczka Academy of Physical Education in Katowice

Who is the main contact?
Dr Ewa Kucio, e.kucio@awf.katowice.pl

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
2-XI/2024

Study information

Scientific Title
Evaluation of the influence of selected gene polymorphisms on the effectiveness of cardiac rehabilitation in combination with pharmacotherapy in heart failure patients with reduced left ventricular ejection fraction

Acronym
CRPGen HF

Study objectives
Polymorphisms of ACE (rs4340, I/D), TNF-α (rs1800629, -308G/A and rs1799964, -1031 T/C), eNOS (rs1799983, 894G/T; rs2070744, -786T/C and a tandem repeat polymorphism in exon 4: 4A /4B) and BNP (rs198389, -381T/C) in heart failure patients with reduced left ventricular ejection fraction (HFrEF) may influence the effectiveness of cardiac rehabilitation combined with pharmacological treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 07/11/2024, University Bioethics Committee for Scientific Research at the Jerzy Kukuczka Academy of Physical Education in Katowice (Mikołowska 72A, Katowice, 40-065, Poland; +48 (0)32 2075352; komisjabioetyczna@awf.katowice.pl), ref: 2-XI/2024

Study design
Multi-centre observational cohort study

Primary study design
Observational

Study type(s)
Other, Quality of life, Efficacy

Health condition(s) or problem(s) studied
Heart failure with reduced left ventricular ejection fraction

Interventions
After patients have qualified for the study and agreed to participate in the biomedical experiment, 10 ml of blood will be taken from an ulnar vein of each patient, in which the following will be analysed:

DNA genomes which will be extracted from peripheral blood leukocytes. Polymorphism of genes [ACE (rs4340; I/D), TNF-a (rs1800629, -308G/A and rs1799964, -1031T/C), eNOS (rs1799983, 894G /T; rs2070744, -786T/C and tandem repeat polymorphism in exon 4: 4A/4B) and BNP (rs198389, -381T/C) will be detected by polymerase chain reaction and after digestion of the amplified DNA sequence with a restriction enzyme. Detection of gene polymorphism will be performed by the Molecular Research Laboratory of the Institute of Physiotherapy and Health Sciences Sciences [Laboratorium Badań Molekularnych Instytutu Fizjoterapii i Nauk o Zdrowiu].

The serum remaining after centrifugation will be used to determine NT-proBNP, TNFa, and CRP concentrations.

In addition, each patient will be assessed for:

1. Exercise tolerance which will be assessed by means of:

1.1. 6-minute walk test (6MWT),

1.2. Submaximal (85% HRmax) treadmill exercise test according to the classic Bruce protocol.

The following indices will be analysed during the test: test duration [min], distance covered [m], the MET energy expenditure, resting heart rate (HRS) and peak heart rate (85%HRmax), (85% HRmax), systolic systolic blood pressure (RRs) and diastolic blood pressure (RRr) at rest and at peak exercise.

2. Left ventricular systolic and diastolic function will be assessed by echocardiography (UKG).

The following indices will be analysed: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF). In addition, Tissue Doppler Imaging (TDI) indices will be assessed: A-wave (diastolic function mechanism during atrial contraction), E-wave (diastolic function mechanism during the rapid ventricular filling phase), elateral (early diastolic velocity of the lateral part of the mitral annulus), eseptal (early diastolic velocity of the medial part of the mitral annulus), E/E (the ratio of the maximum velocity of blood inflow through the mitral annulus during the rapid ventricular filling phase and the maximum velocity of mitral annular motion during the rapid ventricular filling phase), E/A (ratio of early mitral inflow velocity to mitral inflow velocity during atrial contraction), TAPSE (tricuspid annular plane systolic excursion), MAPSE (mitral annular plane systolic excursion).

3. Quality of life will be assessed using the Polish version of the Minnesota Living with Heart Failure Questionnaire (LHFQ) and SF-36 v.2, while self-assessment will be based on the Beck Depression Scale.

4. Physical activity will be measured using the Minnesota Leisure Time Physical Activity Questionnaire and the Paffenbarger Physical Activity Questionnaire.

5. Selected anthropometric parameters such as body weight, height, waist and hip circumference will also be measured.

At the same time, a medication review will be performed by a clinical pharmacy specialist for each patient who participates in the study.

In the following days, patients admitted to the Cardiac Rehabilitation Unit of the Specialist Hospital in Sosnowiec [Wojewódzki Szpital Specjalistyczny Nr 5 im. Św. Barbary] will undergo standard cardiac rehabilitation according to the requirements of the National Health Fund [NFZ].

Patients admitted to the Cardiac Rehabilitation Unit of the Municipal Hospital in Gliwice [Szpital Miejski Nr 4], on the other hand, will be randomly assigned to one of two groups:

The first group (NMESCR) will consist of 50 patients who, in addition to their pharmacological treatment and standard cardiac rehabilitation, will undergo neuromuscular electrostimulation (NMES) 5 times a week (Monday to Friday) for a period of 40 minutes under the supervision of a physiotherapist (15 sessions). NMES will be carried out using an electrostimulation kit. The following muscles will be covered by the NMES: quadriceps (20 minutes) and triceps (20 minutes) of both lower limbs. Electrodes will be applied to the proximal and distal ends of the muscle bellies. An alternating rectangular symmetrical current of 35 Hz will be used. The pulse duration will be 0.4 ms. During the pulse series, an incomplete tetanic contraction of 30-45% of the maximum muscle force will be induced. The duration of the pulse series ('contraction duration') will be 2 seconds and the duration of the interval between the pulse series ('diastole duration') will be 4 seconds.

The second group (CR) will consist of 50 patients who will receive only cardiac rehabilitation, as required by the National Health Fund, as well as pharmacological treatment.

At the end of the 3-week period of inpatient cardiac rehabilitation, the following parameters will be assessed for each patient:

1. Exercise tolerance by 6-minute walk test (6MWT) and submaximal (85% HRmax) treadmill exercise test according to the classic Bruce protocol fficial use

2. Left ventricular systolic and diastolic function by echocardiography (cardiac ultrasound)

3. Quality of life using the Polish version of the Minnesota Living with Heart Failure Questionnaire (LHFQ) and SF-36 v.2. and self-report using the Beck Depression Scale

4. Selected anthropometric parameters such as body weight, height, waist and hip circumference will also be measured.

In addition, 5 ml of blood will also be taken from an ulnar vein of each patient for the assessment of NT-proBNP, TNFa and CRP levels.

A follow-up visit is planned at the end of the study, i.e. 12-16 weeks after the end of the in-patient cardiac rehabilitation, during which the following will be analysed:

1. Quality of life based on the Polish version of the Minnesota Living with Heart Failure

Questionnaire (LHFQ) and SF-36 v.2. and self-report based on the Beck Depression Scale.

2. Physical activity using the Minnesota Leisure Time Physical Activity Questionnaire and the Paffenbarger Physical Activity Questionnaire.

3. Simultaneously, a clinical pharmacy specialist will perform a medication review for each patient.

Intervention Type
Mixed

Primary outcome(s)
DNA genomes which will be extracted from peripheral blood leukocytes. Polymorphism of genes [ACE (rs4340; I/D), TNF-α (rs1800629, -308G/A and rs1799964, -1031T/C), eNOS (rs1799983, 894G /T; rs2070744, -786T/C and tandem repeat polymorphism in exon 4: 4A/4B) and BNP (rs198389, -381T/C) will be detected by a polymerase chain reaction and after digestion of the amplified DNA sequence with a restriction enzyme at one time point

Exercise tolerance will be assessed using the following methods:
1. 6-minute walk test (6MWT)- the distance covered by the subject in meters in six minutes before and after 3 weeks of cardiac rehabilitation combined with pharmacotherapy.
2. Submaximal (85% HRmax) treadmill exercise test according to the classic Bruce protocol. The following indices will be analysed during the test: test duration [min], distance covered [m], the MET energy expenditure, resting heart rate (HRS) and peak heart rate (85%HRmax), systolic blood pressure (RRs) and diastolic blood pressure (RRr) at rest and peak exercise. The test will be performed before and after the completion of 3 weeks of cardiac rehabilitation combined with pharmacotherapy.

Left ventricular systolic and diastolic function will be assessed by echocardiography (UKG) using the following indices before and after a 3-week cardiac rehabilitation combined with drug treatment:
1. Left ventricular end-diastolic diameter (LVEDD)- in mm
2. Left ventricular end-systolic diameter (LVESD)- in mm
3. Left ventricular end-systolic volume (LVESV)- in ml
4. Left ventricular ejection fraction (LVEF)- in %

Quality of life will be assessed using the following measures before and 3 and 12-16 weeks after the completion of cardiac rehabilitation combined with pharmacotherapy:
1. Minnesota Living with Heart Failure Questionnaire (LHFQ)
2. Questionnaire SF-36 v.2
3. Beck Depression Scale

Physical activity will be measured using the following questionnaires before and 12-16 weeks after the completion of cardiac rehabilitation combined with pharmacotherapy:
1. Minnesota Leisure Time Physical Activity Questionnaire
2. Paffenbarger Physical Activity Questionnaire

Anthropometric parameters:
1. Body weight [kg],
2. Height [m],
3. Waist and hip circumference [cm]
Body weight and waist and hip circumference will be measured before and after 3-week cardiac rehabilitation combined with pharmacotherapy.

Key secondary outcome(s))
1. NTproBNP [pg/ml], TNFα [ng/ml], and CRP [mg/ml] blood levels before and after 3-week cardiac rehabilitation combined with pharmacotherapy
2. Medication review measured using patient medical records before and 12-16 weeks after cardiac rehabilitation

Completion date
31/05/2026

Eligibility

Key inclusion criteria
1. Documented heart failure (HFrEF)
2. Echocardiographically determined left ventricular ejection fraction (EF) <50%
3. NYHA class II-IV
4. Clinical stability and no change in treatment within the last month
5. Consent to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
40 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. Unstable ischaemic heart disease
2. Hemodynamically significant aortic valve stenosis
3. Valvular heart diseases requiring surgical repair
4. Complex ventricular arrhythmias
5. Implantation of a cardiac stimulator, cardioverter defibrillator (ICD) and cardiac resynchronisation pacemaker (CRT-D)
6. Acute myocarditis or pericarditis
7. Uncontrolled hypertension
8. Acute thrombosis or embolism
9. Exacerbation of COPD
10. Hepatic or renal insufficiency
11. Lack of consent to participate in the study

Date of first enrolment
01/01/2025

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
Poland

Study participating centre
Cardiac Rehabilitation Unit of the Municipal Hospital No 4 in Gliwice
Zygmunta Starego 20
Gliwice
Poland
44-100

Study participating centre
Cardiac Rehabilitation Unit of St Barbara's Specialist Hospital No 5 in Sosnowiec
Plac Medyków 1

Sosnowiec
Poland
41-200

Study participating centre
The Academy of Physical Education in Katowice
Mikołowska 72A
Katowice
Poland
40-065

Sponsor information

Organisation
Academy of Physical Education in Katowice

Funder(s)

Funder type
University/education

Funder Name
Akademia Wychowania Fizycznego im. Jerzego Kukuczki w Katowicach

Alternative Name(s)
The Jerzy Kukuczka Academy of Physical Education in Katowice, AWF Katowice

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Poland

Results and Publications

Individual participant data (IPD) sharing plan

All data generated and/or analysed during the current study will be available on request from Ewa Kucio (e.kucio@awf.katowice.pl)

IPD sharing plan summary

Available on request