PERSISTENT CARDIAC SYMPTOMS IN PATIENTS WITH ADEQUATLY TREATED GRAVES' DISEASE.

Cardiovascular dysfunction following treatment of hyperthyroidism

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Persistent cardiac symptoms in patients with adequately treated Graves' disease.

General information

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Study background

Hyperthyroidism is a condition with increased production of thyroid hormone from the thyroid gland. The incidence of hyperthyroidism in Denmark is 4,000-5,000 cases per year. Women are four times more likely to get diagnosed with hyperthyroidism then men. The three most common causes of hyperthyroidism are *multinodulous toxic goiter, Graves' disease*, *and solitary toxic adenoma* [Carlé et al. 2011]. Hyperthyroidism affects the heart's inotropy (contractile force) and chronotropy (rhythm) [Dillman 2002; Biondi 2002]. Therefore, patients often experience symptoms such as increased/irregular heart rate, pounding heartbeats, and shortness of breath. The cardiac symptoms often improve when hyperthyroidism is treated and biochemical euthyroidism is achieved [Razvi 2021]. However, knowledge of the long-term effects on the heart is limited. Existing studies have generally shown that patients with hyperthyroidism have an increased morbidity and mortality [Jabbar 2017; Giesecke 2017; Okosieme et al. 2019].

We conducted a questionnaire survey which showed that about 38% of patients with Graves' disease continue to experience cardiac symptoms even months after normalization of thyroid hormone concentrations in the blood. This observation supports the presence of a persistent cardiovascular dysfunction, which may be due to a modulation of genomic or non-genomic factors with an effect on the cardiovascular system [Figure 1]. These reflections are the focus of this clinical study. The aim of the study is to investigate the possible pathophysiology for this new "syndrome" in biochemically euthyroid patients. It is not a repetition of previous similar experiments.

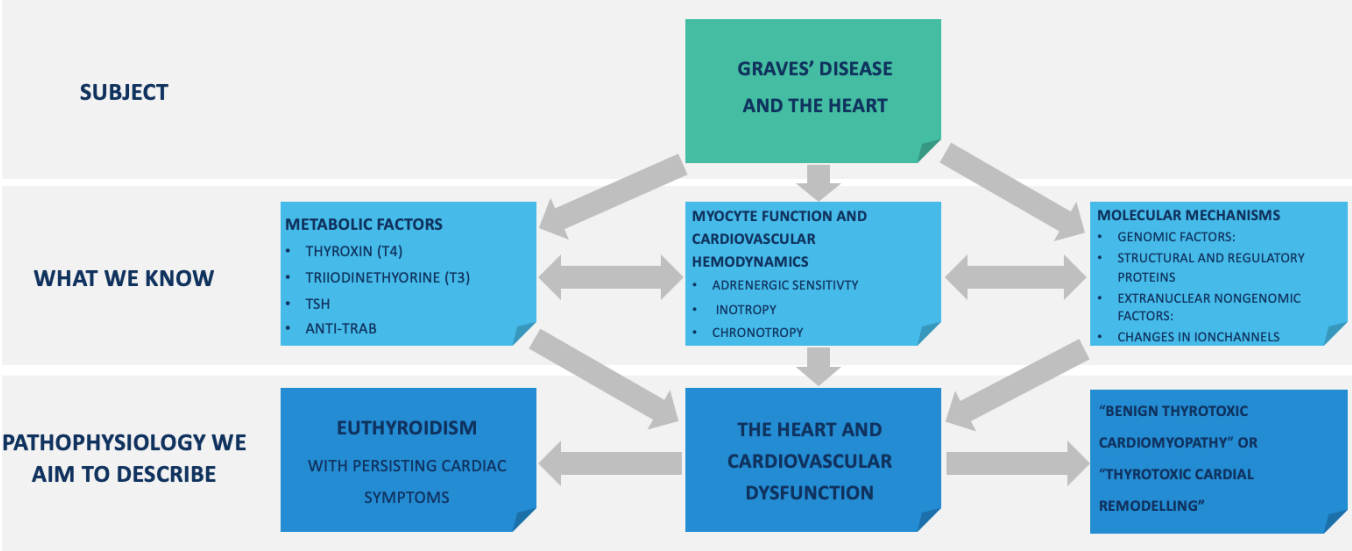

Figure 1. *Visual presentation of a possible pathophysiology in biochemically euthyroid patients with persistent cardiac symptoms during or after treatment with antithyroid medications*

The perspective of the study is to gain knowledge on the clinical presentation of the subgroup of patients with Graves' disease, who experience cardiac symptoms despite achievement of biochemical euthyroidism. In addition, the focus is to examine the mechanisms behind the "syndrome" by clarifying whether there is an objectifiable cardiac dysfunction. The aim is improving clinical practice and drug treatment in the future.

The study is a collaboration between researchers from the Laboratory of Molecular Cardiology (LMC) Department of Cardiology, Rigshospitalet, Department of Biomedical Sciences, University of Copenhagen, Department of Medical Endocrinology,

Rigshospitalet, and Department of Endocrine Diseases, Department of Medicine, Herlev-Gentofte Hospital.

Purpose

The purpose of the study is to characterize patients who are being treated or have been treated for Graves' disease and have been euthyroid for a minimum of three months, but despite this experience cardiac symptoms.

Patient characteristics include:

- Medical history and symptoms
- Biochemical analyses
- A cardiac workup: resting 12-lead ECG, 24-hour ambulatory electrocardiogram monitoring (Holter analysis), transthoracic echocardiography, and an exercise stress test
- Phenotype/genotype variations

No deviations from standard treatments will be made in the study.

Hypothesis

The hypothesis is that Graves' disease in genetically predisposed individuals will induce cardiac changes that persists months to years after normalization of thyroid hormone concentrations in the blood. This is a previously undescribed condition that could be caused by a remodeling of myocardial tissue and of the autonomic nervous system.

Rationale for the study

Euthyroid patients with a persistent tendency to dyspnoea, intermittent palpitations, and increased heart rate – after treatment of Graves' disease – may have a previously undescribed "syndrome" (cf. textbooks and literature in the reference list (page 19)).

Genetic analyses and statistical considerations

We will use the Polygenic Risk Score (PRS), developed on genetic data from the Næstved Cohort (see page 9) and other cohorts to try to predict who is genetically predisposed to e.g. sinus node and contractile dysfunction. The genetic variants included will be selected

using an algorithm that tries to ensure that each genetic variant is independent. Here, the so-called "pruning and thresholding" method is used [Khera AV 2018].

Unfortunately, there is still very little experience with this type of study in multifactorial diseases such as thyrotoxicosis. Given that the study examines an extremely selected phenotype (due to inclusion and exclusion criteria), and the standard deviation (variance) cannot be predicted with certainty, the strength calculation is expected to be subject to uncertainty. Assuming that the standard deviation is 10, alpha is 0.05, cases 80 and controls 200, there will be 80% power to detect a genetic variant with an Odds Ratio of 5 between cases and controls. This is considered to be a clinically relevant difference between the two groups.

Methods

Participants and recruitment

Participants are recruited from the Endocrinology Outpatient Clinic at Rigshospitalet and Herlev/Gentofte Hospital. A list of the departments' patients with a diagnosis of thyrotoxicosis (ICD 10 E05) is extracted. By screening medical records and ICD10 codes it will be possible to select potential participants with Graves' disease. However, there is a risk that some patients are not identified by the above mentioned extraction due to incorrectly registered ICD 10 codes. Therefore, an extraction will be made from the Department of Clinical Biochemistry of all patients in the relevant age group with positive "Thyrotropin Receptor Antibody (TRAb) since 01.01.2014. Hereby, identifying as many patients with Graves' disease as possible. The latter screening method can be initiated once the ethical approval has been obtained.

Patients meeting the following inclusion and exclusion criteria will then be sent a questionnaire with questions about whether the person has persisting cardiac symptoms (Appendix 1). Following the recommendation of the Research Ethics Committee, it is decided to also enclose a copy of the participant information. The potential trial participant is made aware that if they are interested in participating after reading the participant information, they must send a completed questionnaire back to us. Once the questionnaires have been returned, patients with persistent cardiac symptoms will be contacted either by telephone or by letter in the e-health platform.

Inclusion criteria

Patients with Graves' disease between the ages of 18 and 55 years at study entry who #) have been euthyroid for at least three months prior to inclusion and ##) experience one or more cardiac symptoms.

#) Blood tests are used to assess euthyroidism:

i) Normal S-Thyrotropin [TSH] levels [0,4 – 4,8 x E-3 IU/L]

ii) Normal total S-Thyroxin [T4] i] levels [70-140 nmol/L]

iii) Normal free S-Thyroxin [fT4] i] levels [11,5- 22,7 pmol/L]

iv) S-Triiodothyronine [T3] below the upper reference level [2,6 nmol/L]

The above-mentioned criteria are indicative of euthyroidism. However, several conditions (e.g. presence of other disease) and medications (e.g. other hormones, oral contraceptives, amiodarone, recent scans with iodine contrast) can affect the plasma concentrations. Therefore, the assessment of euthyroidism will ultimately depend on an endocrinological evaluation.

##) Patients who in the questionnaire have indicated that they experience:

- Pounding heartbeats

  and/or
- Increased heart rate

  and/or
- Irregular heartrate

  and/or
- Shortness of breath

Exclusion Criteria

1) Cardiovascular disease
2) Deemed unsuitable by project staff (e.g. due to language problems)
3) Pregnancy
4) Alcohol abuse or other abuses

Examination methods

Biochemical analyses

- 60 ml of blood was drawn and transferred to different test tubes with different chemical additives. The blood samples are used for determination of biochemical, hematological and immunochemical parameters in accordance with Rigshospitalet's LabPortal (in casu: S-Hgb, S-Leukocytes, S-ionised Ca2+, S-Na, S-K, S-Creatinine, S-ALAT, S-LDH, S-Alkaline phosphatase, S-bilirubin, S-TSH, S-TT3, S-TT4, S-fT4, S-anti-TPO, S-Tg, S-TgAb, S-TRAb, S-TBG, T4-uptake test, S-SHBG, S-proBNP, S-proANP, S-hsCRP, S-CardiolipinAb, P-Renin, Vitamin D).

Paraclinical, cardiac studies

1. Resting 12-lead ECG (standard ECG): 3 bipolar extremity leads (I, II, and III), 3 unipolar extremity leads (aVR, aVL, and aVF), 6 unipolar precordial leads (V1, V2, V3, V4, V5, and V6). Rhythm (sinus and/or ectopic rhythm), cardiac axis, ECG intervals (RR interval, PQ interval, QRS interval), atrial enlargement and ventricular hypertrophy were noted. ECG is analysed after the V-point analysis [MK 18th ed., page 897].
2. 24-hour ambulatory electrocardiogram monitoring with a small portable recorder and subsequent computer analysis with algorithm for narrow QRS complex tachycardia. Examination for cardiac autonomic neuropathy (abnormal heart rate variation). During the ECG monitoring the patients keep a diary registering palpitations, near-/fainting, shortness of breath and chest discomfort.
3. Transthoracic echocardiography (ultrasound of the heart). The examination provides anatomical information about the pericardium, myocardium, ventricles, heart valves and central vessels, as well as quantitative information about the myocardium's pumping ability, haemodynamics and valve function. The recordings are blinded and analyzed by supervising echocardiographer and consultant Frank Steensgaard-Hansen.
4. The exercise stress test is performed as a physical load test on an ergometer bike with standardized increase (25W at start, 25W increase every 2 minutes) of the workload while simultaneously monitoring symptoms, blood pressure and 12-lead

ECG before, during and after the test. The investigation shall be conducted in accordance with the protocol available on Cardio.dk. The purpose of the study is to assess the development of arrhythmias, the functioning of the autonomic nervous system and work capacity. The maximum heart rate and time to this, resting heart rate, and time from max heart rate to resting heart rate are measured.

Genetic analyses

3 x 9 ml of blood is drawn for genetic analyses. The blood is transferred to EDTA glass and glass with Trasylol and frozen and stored at -80 degrees. Purification of DNA is performed at the Laboratory of Molecular Cardiology, Rigshospitalet Heart Center, using the Maxwell 16 LEV blood DNA Kit (sold by Promega; Wisconsin, USA). Later, genotyping is carried out using ChIP technology at the *Institut für Klinische Molekularbiologie, Universitätsklinikum,* Schleswig-Holstein, Kiel, Germany. This is not a whole-genome sequencing study. The study aims to investigate single nucleotide polymorphisms (SNP) in specific regions of the genome. The study uses SNP-array/SNP genotyping, where the analysis is based on general genetic variation and not mapping of the genome. The results are used to map risk loci and to determine plausible disease-causing genes. The study will give an understanding of the most common variants in Graves' patients, and with the possibility of comparing these with the Næstved cohort and the United Kingdom Biobank (UKBB) as well as being able to compare the variants with control groups. The aim of the study is to determine the significance of the sum of genetic variants' for the development of disease, called the Polygenetic Risk Score.

Excess biological material is sent back to Denmark when the analyses in Germany have been carried out. The material is then stored in a biobank, see page 10.

Analyses of participants are compared with analyses of Graves' patients from the Næstved cohort

- The trial participants with Graves' disease will undergo genotyping and the results of this will be compared with findings of variants determined in 20,000 of a general population of 70,000 individuals (the Næstved cohort which has been followed over 20 years) in which the incidence of Graves' disease is about 25 out of 100,000 per year (The project is approved in VEK SJ-114). The Næstved cohort is an already genotyped (SNP-genotyped, not whole-genome) cohort of patients. Members of our research group are the managers of the Næstved project. Therefore, it is in our

interests to compare genetic variants found in Graves' patients with a control cohort that we already know and have previously genotyped. Consent is not obtained from the participants of the Næstved cohort because no new studies of the participants' genome are carried out. Thus, there are no health consequences for the Næstved cohort's patients' participation in this project, nor elements of a research perspective that the patients must consider.

- Variants found are further verified using data from the UKBB on about 500,000 individuals. The UKBB contains clinical and genetic data on 457 patients with Graves' disease. There is no question of importing biological material from these patients. Through a data agreement with UKBB, our research group has access to anonymised patient information on British individuals. This includes SNP genotyping, MRI scans, ECGs, etc. Hereby, the data agreement enables us to compare our results with similar patients.

Biobank

Blood samples will be pseudoanonymized and stored for later supplementary genetic, biochemical, histological, and other pathoanatomical studies. Thus, a research biobank will be established in connection with the project. At the end of the project, the biological material will be stored in a fully anonymized manner at the Laboratory of Molecular Cardiology in a conventional biobank. The biological material will be stored for 20 years and will only be included in further research projects with the consent of the participants or with an exemption from the consent given by the research ethics committee. The data protection rules are complied with when any type of biological material is stored in our biobank.

Study design

Visit 1: Informative visit, anamnesis, and paraclinical examinations

The purpose of the visit is to check whether the potential participant meets the criteria for participating in the study and to inform the participant about the study prior to any consent. The potential participant has received a telephone call prior to the visit (see above) where the questionnaire is discussed. Furthermore, the trial participant has received written information on the study (appendices 1 and 2). The informative visit and examinations can be carried out during the same visit, which takes place at the LMC. This is provided that

the participant gives his/her consent immediately after the informative meeting. If the potential participant wishes 24-hour reflection time another meeting will be arranged for blood tests and ECG. The duration of the meeting is approximately 1 hour and includes:

1) Oral information, clarification of any questions
2) Conversation about informed consent and 24-hour reflection time
3) The signature of informed consent is ensured before any examinations
4) Questions concerning:
    - Inclusion and exclusion criteria
    - Medical history related to Graves' disease (onset, duration, treatment, family history, associated Graves' orbitopathy, smoking)
    - Medicine
    - Symptoms
    - Other diseases
5) Further classification of cardiac symptoms through a questionnaire regarding grading of the symptoms.
6) Objective examination including blood pressure, height, and weight
7) Blood samples for biochemical and genetic analysis
8) 12-lead resting ECG

Visit 2:

The visit takes place at LMC, lasts approximately 1 hour, and includes:

1) Echocardiography
2) Attachment of ECG electrodes connected to a recorder for 24-hour ambulatory electrocardiogram (Holter)

Visit 3:

The visit takes place at the Cardiology Outpatient Clinic, Section 2003, Rigshospitalet. It lasts approximately 1 hour and includes:

1) exercise stress test

Visit 4:

The visit takes place at the Endocrinology Clinic, lasts approximately 1 hour, and includes:

1) Information about the results of the cardiac examinations
2) Conversation about the possibilities of drug treatment

Visit 5:

The visit takes place at the Endocrinology Clinic, lasts approximately 1/2 hour, and includes:

1) Information about the results of the genetic tests
2) Follow-up

Study duration
Recruitment of patients will start as soon as ethical approval is obtained from the research ethics committee. The study is expected to be completed within 5 years.

Informed consent

Patients who wish to participate in the study will receive a letter with further information (Appendix 1 "Questionnaire"). Attachments to the letter include a written participant information (Appendix 2, “Participant information”), the *“before you decide”* brochure, and the *“Rights of participants in a research study”* brochure. The letter states that the participant can contact us by phone, e-mail, or letter if he/she is still interested. When the participant contacts us, further information will be provided by the project staff about the time, place and first meeting. All conversations, personal as well as telephone, will be organized so that the informing doctor/medical student is not disturbed during the conversation. Plenty of time is set aside to answer questions. During the first telephone conversation the participants are informed that they have the right to bring a family member/friend/acquaintance.

Risks, side effects and drawbacks

The blood samples are drawn as a regular blood sample from a vein in the arm. Approximately 90 ml of blood is drawn. The total amount of blood is equivalent to 20% of what a blood donor has drawn. The body quickly restores this amount. Thus, it is a small

amount of blood. However, it can seem like a lot due to the many test tubes. There will be a small risk of bruising and minor pain, as well as a small risk of infection.

The electrocardiogram and ultrasound scan may be associated with minor discomfort. Some people may experience skin irritation due to the ECG electrodes. It may also be necessary to shave the chest. Transthoracic echocardiography gel may cause irritation. In addition, discomfort can also occur when the probe is passed over the skin and e.g. along the ribs. Patient safety in the event of symptom-limited maximum work testing is high. The risk of complications is lower than for patients with suspected ischemic heart disease (1 per 10,000 studies). The examinations are carried out by trained personnel and performed in a room with equipment to counter serious heart rhythm disturbances.

There is a risk that that we may encounter random findings during the genetic screening in the form of genetic predisposition to other and more serious diseases. The project group has the competencies to assess the significance of most of these findings. If not, the relevant expert will be contacted. Unless the trial participant has opted out, he or she will be informed of these findings if:

- there is a reasonable probability that a genetic predisposition is present,
- there is a definite documented correlation between the genetic predisposition and the development of the disease,
- the disease can be significantly prevented or treated.

Ethical aspects

Informed consent

During the informative meeting the potential participant will receive oral information from the project staff. Oral information will be given in private, undisturbed. The potential participant will be informed of the right to bring a family member/friend/ acquaintance. The participant will receive both written and oral information about the study's purpose, examinations, potential risks and discomfort, and expected benefits. If the participant wants additional reflection time or wishes the presence of a family member/friend/ acquaintance, a new informative visit will be scheduled (after more than 24 hours). Written

informed consent from participants will be obtained prior to the start of the study. The project staff has ensured that the participants receive comprehensive information about the study and that they are available to the participants by telephone (9-15 every weekday), email (response within 24 hours on weekdays), and letter.

Processing of personal data

Processing of personal data before the participants have given their consent to participate:
Data will be extracted via the laboratory portal LabKA which is connected to the e-health platform. A screening for positive “TRAb” is performed. In addition, a search for relevant diagnostic codes will be performed to identify patients with hyperthyroidism followed at the department of Endocrinology at Rigshospitalet or Herlev-Gentofte Hospital. Medical records are reviewed. Blood test results and imaging are used to identify patients with Graves’ disease. Blood test results and medication are then reviewed to determine whether the patients meet the inclusion and exclusion criteria.

After informed consent has been obtained:
The medical record will be reviewed to obtain relevant blood test results and to inform participants about changes in medication during the trial period. Information obtained prior to consent is passed on from the doctor responsible for treatment to the doctor responsible for research.

Consent gives the project staff direct access to the patient's medical record to obtain information about the participants health conditions. In addition, the consent also gives relevant control authorities access to the patient record as part of the statutory control and inspection of the research project, which they are obliged to carry out.

The General Data Protection Regulation and the Data Protection Act will be complied with. Direct personal data is not sent abroad.

Data will only be personally identifiable to doctors/medical students involved in the project. After the end of the study, data will be stored in anonymised form on Rigshospitalet's server for 15 years.

DNA to Germany

DNA samples are sent as pseudo-anonymized samples. It ensures that personal data is only known to the project staff. The samples are sent with a pseudo-number. The results

from our scientific partner at Kiel University Hospital are returned with the same pseudo number. Only the project staff possesses a translation key that matches the pseudo-number with personal data.

At the Laboratory of Molecular Cardiology, there is already a data processing agreement with our partners regarding arrhythmias. This data processor agreement can be found under the ethical approval number H-A-2008-004. As soon as the application for ethical approval has been sent, a new data processing agreement is prepared for this project. The agreement is sent to The Research Ethics Committees immediately afterwards. Please also note that Chapter V of the General Data Protection Regulation is complied with when the project material is being sent abroad.

Possible benefits for trial participants

Benefits from participating in the study may include better medical treatment of their cardiac symptoms in the future. The cardiac symptoms in the patient group are associated with discomfort. Therefore, improvement in the symptoms may improve their quality of life.

Possible benefits for research and others

The results of the study are expected to increase our understanding of the pathophysiology behind cardiac symptoms in euthyroid patients treated for hyperthyroidism. The study could potentially contribute to better treatment strategies in the future.

Risk/benefit assessment

The trial entails very few inconveniences and risks for the participant, who in turn can benefit from participating. Since we work with frequent gene variants, there is a very small risk of uncovering genetic predisposition to serious disease. The trial participants have decided for themselves whether they want to be informed about such findings. The research group has extensive experience in advising patients about these types of diseases. The trial is expected to have great potential for advancing science. Therefore, we believe that the advantages of the trial far outweigh the disadvantages.

The study will be carried out in accordance with the Helsinki Declaration.

Rights of participants

The participant may at any time, orally, in writing or by other clear statement, withdraw his/her consent to participate, and withdraw from the research project. If the participant withdraws his/her consent, this does not affect the right to current or future treatment or any other rights that the participant may have. In addition, standard information on rights of participants is sent to potential participants.

Information on health conditions, private information, and other information is kept confidential. Information, including information about blood samples and tissues, is stored in accordance with the Danish Health Act, the General Data Protection Regulation and the Danish Data Protection Act.

It is possible to gain access to trial protocols in accordance with the Access to Public Administration Files Act. This means that the participants can get access to all papers regarding participation in the study.
It is possible to complain and receive compensation in accordance with the Act on Access to Complaints and Compensation within the Health Service. If an injury should occur during the trial, you can contact the Danish Patient Compensation, take a closer look at www.patienterstatningen.dk

Study site

The planned examinations will be carried out at the Laboratory of Molecular Cardiology, Cardiology Clinical, Rigshospitalet and at LMC, Department of Biomedical Sciences, University of Copenhagen. The genetic analysis takes place at the *Institut für Klinische Molekularbiologie, Universitätsklinikum,* Kiel, Germany. The biochemical analyses are carried out at Rigshospitalet, Department of Clinical Biochemistry, Diagnostic Center. The paraclinical examinations will be carried out partly at the Laboratory of Molecular Cardiology, Rigshospitalet and partly at the Department of Cardiology, Rigshospitalet.

Economy

The initiators of the project are Professor Emeritus, Dr.med. Stig Haunsø and Professor, dr.med. Ulla Feldt-Rasmussen, as well as researchers from the Laboratory of Molecular Cardiology, Department of Cardiology, Rigshospitalet. It must be stated that no researchers have financial ties to the grantor or other interests in the experiment. Supporters for this project are; The John and Birthe Meyer Foundation and Villadsen Family Foundation. The laboratory covers the rest of the expenses. If additional financial support is applied for, please note that the Research Ethics Committees and the trial participants will be informed of future funding.

Remuneration or other benefits for participants

No remuneration is paid for participating in the study. Nor are any other benefits given for participation. Transport expenses are covered on request. No one will receive compensation for inconvenience, as it is estimated that no interventions or examinations cause any inconveniences greater than those that may occur during a regular visit to their own doctor or specialist.

Budget

The project's starting budget is DKK 476,000. The equipment used for the cardiac examinations is available at the LMC or at the Cardiology Clinic. Below is a list of the expected expenses and their costs.

Budget	Singular price (DKK)	Total price (DKK)	Currently paid (DKK)
Biochemical analyses	3,125	250,000	X
Exercise stress test	700	56,000	X
Echocardiography	600	48,000	X
Holter analysis	200	16,000	X
DNA-analysis	200	16,000	X
Other	N/A	90,000	X

Figure 2. *Overview of budget.*

The start-up budget is financed with research funds from a multi-year grant from The John and Birthe Meyer Foundation to Professor Stig Haunsø, Laboratory of Molecular Cardiology, Department of Cardiology, Rigshospitalet. The funds are used in accordance with the indicated budget.

In addition, it should be mentioned that approximately DKK 80,000 from private foundations granted from other foundations helps to pay the salaries of academic staff. This is not included in the project's start-up budget.

Publication and copyright

Both positive, negative and neutral results will be published, the latter either on www.clinicaltrials-gov or on www.clinicaltrialsregister.eu

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