Evaluation and testing of the microvascular function in asymptomatic athletes

Published: 08-06-2017
Last updated: 12-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON44625

Source
ToetsingOnline

Brief title
ESTIMATE

Condition

- Myocardial disorders

Synonym
Microvasculair function, the function of the smaller cardiac blood vessels

Research involving
Human

Sponsors and support

Primary sponsor: Cardiologie
Source(s) of monetary or material Support: Subsidie aangevraagd bij en toegezegd door: Stichting Vrienden van het Hart Zuidoost Brabant. Sport Medisch Advies Centrum

Veldhoven

Intervention

Keyword: Athletes, Microvascular function, PET-CT

Outcome measures

Primary outcome

* Myocardial blood flow (MBF) per gram of myocardial tissue (ml/min/g) with

82Rb PET-CT imaging.

* Myocardial flow reserve (MBF at peak hyperaemia / MBF at rest) with 82Rb

PET-CT imaging.

Secondary outcome

* The plasma levels of eNOS and ET-1 in athletes with a normal and abnormal

exercise test result.

Study description

Background summary

Regular aerobic exercise has been shown to reduce the risk for fatal and non-fatal cardiac events and is therefore highly recommended both for healthy subjects and patients with cardiovascular disease. However, in selected cases, acute vigorous exercise may also be the trigger for a potential fatal cascade leading to myocardial infarction or sudden cardiac death (SCD). In order to reduce the burden of (fatal) cardiac events, the use of pre-participation screening is recommended for athletes to detect potential causes of (fatal) cardiac events an early stage. Exercise electrocardiography is particularly recommended to detect obstructive coronary artery disease (CAD). However, in many athletes (up to 95%) with an abnormal exercise test result, no obstructive CAD is found during further diagnostic evaluation such as myocardial perfusion imaging and/or coronary angiography. As the pathophysiology of an abnormal exercise test in the absence of obstructive CAD among athletes remain unknown, uncertainty exists with respect to prognostic implications in these athletes, and, in addition, it leads to therapeutic dilemma*s. Based on preliminary (animal) studies, possible explanations may be an inadequate increase in

myocardial capillary density in response to development of training-induced myocardial hypertrophy or coronary microvascular dysfunction due to remodeling of intramural coronary arteries. Both mechanisms will eventually result in an insufficient myocardial blood supply during exercise and may therefore serve as a trigger for a cascade leading to myocardial infarction or potentially lethal arrhythmias. More knowledge on the pathophysiological mechanisms in humans will eventually lead to better diagnostic and therapeutic strategies in this population.

Study objective

The main objective of this study is to evaluate whether myocardial ischemia in the absence of obstructive CAD in athletes is associated with a reduced myocardial perfusion when compared to control subject with a low a priori risk of CAD and without the presence of epicardial coronary artery disease. The secondary objectives are to evaluate whether myocardial ischemia in the absence of obstructive CAD in athletes is associated with a different levels of the precursor endothelial nitric oxide synthase (eNOS) and endothelin-1 (ET-1) when compared with the control subjects

Study design

A single-center prospective observational case-control study among asymptomatic recreational and competitive athletes who underwent pre-participation screening at the department of Sports Medicine of Máxima Medical Center and/or visited the department of Cardiology of Máxima Medical Center. Athletes with an abnormal exercise test and abnormal myocardial perfusion scintigraphy (MPS) indicating myocardial ischemia within the last five years but without epicardial coronary artery disease will be selected. These athletes will be compared with a gender and age-matched historic control group consisting of individuals with a low a priori risk and without the presence of significant epicardial CAD who already underwent 82Rb PET / CCTA as part of standard diagnostic procedure, using a database from the same hospital. All athletes and control subjects will undergo a blood test. Only athletes will undergo 82Rb PET and coronary computed tomography angiography (CCTA).

Study burden and risks

At a population level, the results of this study will lead to a better understanding of microvascular coronary (dys)function in asymptomatic athletes. Consequently, this may lead to an increased insight in a potential pathological substrate in athletes with concordant abnormal results as these athletes could be prone to suffer cardiac (lethal or non-lethal) events and should be advised to refrain from vigorous exercise. Also, a better understanding of the underlying pathophysiological mechanisms will eventually lead to increased insights in therapeutic and prognostic consequences. In that way, athletes can

be provided with a tailored treatment and advice with respect to continuation of sports activities. For the individual athlete, the results of this study will provide a more precise assessment of the extent of myocardial ischemia. In case of other abnormal findings (e.g. coronary artery disease), the subject will be referred to their own general practitioner with a recommendation for referral to a cardiologist. If the subject is currently being treated by a cardiologist, a direct referral will be initiated and the subject will be treated according to the current standards. For healthy control subjects, there is no direct individual benefit. these subjects will only undergo blood tests at Máxima Medical Center. The risks of a direct venipuncture are hematoma and bleeding at the site of puncture, in very exceptional cases thrombophlebitis.

Only athletes with documented myocardial ischemia (N = 10) will undergo 82Rb PET / CCTA and will be exposed to radiation with a total effective radiation dose of approximately 5.8 * 7.1 mSv. Prior to the 82Rb PET / CCTA, two intravenous lines will be placed which are both required (1 line for administration of 82Rubidium and 1 line for administration of Adenosine). Risks of an intravenous line are minimal and comparable to a normal direct venipuncture (see above). Rubidium is generator produced potassium analog with physical half-life of 76 seconds and the administration in humans for the measurement of myocardial blood flow first occurred in the early 80s. With increased PET/CT systems, the number of patients grew but it still represents only a small percentage by comparison with the use of 99mTc-sestamibi. No adverse effects of administration of Rubidium are known. Adverse effects that are described during adenosine administration are bradycardia, premature atrial or ventricular beats, dyspnea, blushing, nausea and vomiting. All side effects disappear immediately when administration is discontinued. Adenosine has been used for many years worldwide in pharmacological myocardial stress testing and has a well-established safety record. It has a minimal effect on heart rate and blood pressure during continuously perfusion and leads only to a modest increased oxygen requirement. The department of Nuclear Medicine of the Jeroen Bosch Hospital is also using Adenosine during 82Rb PET for many years. Therefore, staff and personnel members are well experienced with the use and potential side effects of Adenosine infusion. Athletes are continuously monitored during administration and if serious side effects occur; administration will be discontinued immediately.

All athletes with documented ischemia will be subjected to an effective radiation dose of 5.8 * 7.1 mSv. When compared to the 2.6 mSv annual radiation exposure from natural sources in the Netherlands (36), this is a 2.2 to 2.7-fold increase in radiation exposure. A previous study showed that there is an increased non-fatal cancer risk of 0.01% per mSv of exposure to radiation (37), leading to an increased risk of non-fatal cancer of 0.058 * 0.071% in the participating athletes. In order to avoid a high cumulative dose the use of radiation should be minimized. In this perspective, other non-invasive modalities to investigate the microcirculation were considered. Perfusion MRI is one of these modalities. The main advantage of this procedure is that MRI

does not use ionizing radiation. However, PET is currently the golden standard for the assessment of microvascular function due to the highly accurate myocardial blood flow quantification (38). In contrast with 82Rb PET, absolute measures of rest and stress flow with perfusion MRI did not correlated well. Also, robust fully-quantitative models have been developed only in experimental settings. Due to these limitations, visual assessment of the myocardial perfusion remains clinically the most used analysis tool when cardiac MRI is used (39). In the present study, the main study parameters are myocardial blood flow and flow reserve. As accurate quantitative measurements are needed, these parameters can only be obtained via PET-82Rb in the current clinical practice.

Coronary CT will be used to obtain anatomical imaging of the coronary arteries. This non-invasive modality can accurately detect and exclude the presence of epicardial CAD. As epicardial CAD may induce an impaired myocardial blood flow, it is necessary to rule out its presence. In this way, the calculated myocardial blood flow and flow reserve via 82Rb PET / CCTA will solely reflect the microvascular function. The index athletes underwent coronary angiography (CAG) as part of the diagnostic procedures. However, this CAG is performed months to years before recruitment for the present study. Therefore, as CAD at the time of study enrollment cannot be ruled out with certainty, the coronary anatomy will be evaluated also at the time of study enrollment.
For this purpose, 82Rb PET will be combined with a CCTA scan, which imposes an additional radiation dose of 3.4 * 4.1 mSv which is lower than the radiation dose of CAG (5 * 7 mSv).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Index group: asymptomatic athletes with concordant abnormal exercise electrocardiography results and abnormal myocardial perfusion scintigraphy results but without the presence of epicardial coronary artery disease. ;An athlete is defined as a sportsmen who is engaged in sports for at least 2.5 hours a week for a period of minimally 30 weeks per year or in two or more sports with a minimum of 1.5 hours per week within one type of sports for at least 20 weeks per year;Control group: Individuals with a low a priori risk of CAD and without presence of significant epicardial coronary artery disease who last year already have undergone PET/CT as part of a prior diagnostic procedure.

Exclusion criteria

Symptomatic athletes ((Exercise induced) chest pain, palpitations, dizziness, light headiness or syncope), athletes with epicardial coronary artery disease, athletes with previous myocardial infarction

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2017
Enrollment:	22
Type:	Actual

Ethics review

Approved WMO

Date:	08-06-2017
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL61679.015.17