Regulation of muscle oxidative phenotype by hypoxia in Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF)

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26311

Source
NTR

Brief title
N/A

Health condition

COPD, chronic heart failure
hypoxemia, skeletal muscle dysfunction

Sponsors and support

Primary sponsor: Maastricht University (transnationale Universiteit Limburg)
Source(s) of monetary or material Support: Maastricht University (transnationale Universiteit Limburg)

Intervention

Outcome measures

Primary outcome

1. Main outcome parameters are the expression levels of HIF-1á, PGC-1 and PPARs (before and after exercise), which will be measured at protein and mRNA level by western blotting and PCR respectively;

2. Also, markers of hypoxia such as vascular endothelial growth factor (VEGF), carbonic anhydrase-9 (CA-9) and heme oxygenase-1 (HO-1) will be investigated using real time PCR;

3. Beside this, metabolic enzyme activities (citrate synthase, â-hydroxyacyl-CoA dehydrogenase, phosphofructokinase) and muscle fiber type proportions will be determined to assess muscle oxidative phenotype;

4. Main outcomes in the adipose tissue biopsies comprise of adipocyte size, gene expression levels of inflammatory and hypoxia-related genes and adipose tissue macrophage infiltration.

Secondary outcome

Secondary outcome parameters are skeletal muscle function and exercise capacity.

Study description

Background summary

Rationale:

Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF) are major causes of morbidity and mortality throughout the world. These chronic diseases are not only characterized by their local impairment, but also by their disabling impaired exercise performance. Peripheral skeletal muscle dysfunction has been identified as an important contributor to exercise intolerance. Muscular impairment involves a slow-to-fast shift in fiber types and a reduced oxidative capacity of the skeletal muscle cells. It is likely that muscle hypoxia is a major determinant of these processes, considering the fact that chronic or exercise-induced hypoxemia and underperfusion are obvious features of COPD and CHF respectively. Positive key mediators of muscle oxidative metabolism and slow twitch fiber phenotype are peroxisome proliferator-activated receptors (PPARs) and PPARã co-activator-1 (PGC-1) whereas hypoxia-inducible factor-1á (HIF-1á) is an important mediator in hypoxia sensing and stimulator of glycolytic metabolism. We hypothesize that muscle hypoxia, either chronic or intermittent (exercise-induced), is responsible for the altered muscle oxidative phenotype in COPD and CHF through modulation of the regulatory molecules PGC-1/PPARs and HIF-1á.

Systemic inflammation is believed to play an important role in COPD. Classically, it has been hypothesized that greater concentrations of circulating inflammatory mediators “spill-over” from the pulmonary compartment. However, for this no convincing evidence has been published. Alternatively, adipose tissue has been described as a potent producer of

inflammation and hypoxia has been proposed to trigger an inflammatory response of the adipose tissue. We hypothesize that COPD patients have greater adipose tissue inflammatory status compared to healthy persons and that hypoxia is a mediator of this inflammatory trigger.

Objective:
The aim of this study is to identify direct markers of muscle hypoxia in COPD and CHF patients in relation to the altered muscle oxidative phenotype and the putative mediators HIF-1á and PPARs/PGC-1. Insight in the underlying molecular mechanisms of the influence of hypoxia on muscle oxidative phenotype may lead to novel intervention strategies to reverse muscle weakness in COPD and CHF.

The second aim of this study is to investigate whether adipose tissue is an extrapulmonary source of inflammation in COPD patients.

Study design:
In this cross-sectional study, muscle biopsies will be obtained before and after exercise and tested for molecular markers of hypoxia. In addition, all subjects will be characterized thoroughly including measurement of lung function, exercise capacity, muscle function and body composition measurement. Fasting adipose tissue biopsies will be obtained in COPD patients and healthy persons.

Study objective

Muscle hypoxia, either chronic or intermittent (exercise-induced), is responsible for the altered muscle oxidative phenotype in chronic obstructive pulmonary disease and chronic heart failure through modulation of the regulatory molecules PGC-1/PPARs and HIF-1alpha.

COPD is associated with a higher adipose tissue inflammatory status compared to healthy persons which is associated with systemic inflammation.

Study design

Day 1 and day 8.

Intervention

In this cross-sectional study, muscle biopsies will be obtained before and after exercise and tested for molecular markers of hypoxia. All subjects will be characterized thoroughly including measurement of lung function, exercise capacity, muscle function and body composition measurement. In addition, adipose tissue biopsies will be obtained from the COPD patients and healthy persons to investigate adipose tissue inflammatory status.

Contacts

Public
B. Borst, van den
Orbis Medical Center
Department of Respiratory Medicine
6162 BG Sittard-Geleen
Sittard
The Netherlands
+31 (0)43 3881327
Scientific
B. Borst, van den
Orbis Medical Center
Department of Respiratory Medicine
6162 BG Sittard-Geleen
Sittard
The Netherlands
+31 (0)43 3881327

Eligibility criteria

Inclusion criteria

1. COPD patients: COPD according to GOLD criteria.

2. CHF patients: diagnosis heart failure with an ejection fraction <40% determined by echocardiography;

3. Healthy persons.

Exclusion criteria

COPD patients:

malignancy, cardiac failure, distal arteriopathy, recent surgery, severe endocrine, hepatic or renal disorders, oxygen therapy and recent participation in a revalidation program (previous 6 months).

CHF patients:
unstable disease, unstable angina pectoris, correctable cause of heart failure or valvular heart disease, restrictive or hypertrophic cardiomyopathy, malignancy, pulmonary disease

(including primary pulmonary hypertension and COPD), distal arteriopathy, recent surgery, severe endocrine, hepatic or renal disorders and recent participation in a revalidation program (previous 6 months).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non controlled trial

Control: N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2008
Enrollment:	90
Type:	Actual

Ethics review

Positive opinion

Date:	11-08-2008
Application type:	First submission

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
NTR-new	NL1342
NTR-old	NTR1402
Other	: MEC 08-2-059
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A