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

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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/...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON26311

Bron
NTR

Verkorte titel
N/A

Aandoening

COPD, chronic heart failure
hypoxemia, skeletal muscle dysfunction

Ondersteuning

Primaire sponsor: Maastricht University (transnationale Universiteit Limburg)
Overige ondersteuning: Maastricht University (transnationale Universiteit Limburg)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksopzet

Day 1 and day 8.

Onderzoeksproduct en/of interventie

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.

Contactpersonen

Publiek

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

Wetenschappelijk

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

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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).

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm

Controle: N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-10-2008
Aantal proefpersonen:	90
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	11-08-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1342
NTR-old	NTR1402
Ander register	: MEC 08-2-059
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
N/A