Regulation of muscle oxidative phenotype by hypoxia in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON33801

Source
ToetsingOnline

Brief title
Regulation of muscle oxidative phenotype

Condition

- Heart failures
- Muscle disorders
- Respiratory disorders NEC

Synonym
heart failure, lung emphysema

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: COPD, hypoxia, metabolism, muscle

Outcome measures

Primary outcome

Main outcome parameters are the skeletal muscle expression levels of HIF-1α,

PGC-1 and PPARs in the different groups.

Secondary outcome

Also, markers of hypoxia such as vascular endothelial growth factor, carbonic

anhydrase-9 and heme oxygenase-1 will be measured. Metabolic enzyme activities

and muscle fiber type proportions will be determined to assess oxidative

phenotype. Outcome parameters regarding adipose tissue are adipocyte size and

cell surface, expression levels of markers for hypoxia like HIF-1α and GLUT-1,

and expression levels of inflammatory mediators like TNF-α, IL-6, leptin and

adiponectin.

Study description

Background summary

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 PPARγ co-activator-1 (PGC-1) whereas hypoxia-inducible factor-1α (HIF-1α) 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-1α.
Another possible mechanism by which hypoxia may affect muscle oxidative capacity could be indirectly through a cross-talk with adipose tissue. Adipose tissue has been shown to be an active producer of inflammatory mediators, like TNF-α, IL-6, leptin and adiponectin. It is also well described that hypoxia in adipose tissue, either as an effect of hypoxemia or defects in fat tissue itself, results in an enhanced pro-inflammatory cytokine release. Recent unpublished data from our lab clearly show that TNF-* leads to a loss of oxidative phenotype in cultured muscle cells and in COPD increased TNF-α expression in skeletal muscle cells was associated with impaired oxidative capacity of these cells. Since both COPD and CHF are highly associated with systemic inflammation, we hypothesize that excessive release of inflammatory mediators by adipose tissue due to hypoxia could also affect the oxidative capacity of skeletal muscle cells in COPD and CHF.

Study objective

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

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 undergo an adipose tissue biopsy that will be histologically investigated and tested for markers for hypoxia and inflammation. Patients will be characterized thoroughly including measurement of lung function, exercise capacity and muscle function.

Study burden and risks

Subjects that participate in this study will be asked to come to the hospital

twice. During these visits, they will undergo lung function testing, measurement of height, weight, whole-body fat free mass and muscle function. Blood flow in the arm is measured by venous occlusion plethysmography. Subjects will have to fill in a questionnaire and wear an accelerometer for one week. One adipose tissue biopsy will be taken at rest, and one or two muscle biopsies will be taken in combination with an exercise test (cycle ergometry). Before and during the exercise test, an electrocardiogram will be made and muscle oxygenation will be measured by an infra-red probe. A venous blood sample will be taken from all subjects for determination of oxygen markers and markers for inflammation. Minor risks are associated with the muscle biopsy. These risks include subsequent bleeding, muscle aching, infection and minor nerve damage. The minor risks associated with an adipose tissue biopsy are subsequent bleeding, minor nerve damage and infection. Drawing of arterial blood from the radial artery can be associated with bleeding and minor nerve damage. Subjects do not benefit personally from participating in this study, but contribute to research that might be beneficial for large patient groups in the future.

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

COPD patients: inclusion criterion for COPD patients is COPD according to GOLD criteria.
Heart failure patients: inclusion criterion for CHF patients is diagnosis heart failure with an ejection fraction < 40% determined by echocardiography

Exclusion criteria

COPD patients: exclusion criteria for COPD patients are 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: exclusion criteria for CHF patients are 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). Patients with artificial valves, known left ventricular thrombi and mitral stenosis will also be excluded.

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):	12-03-2009
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	06-10-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-03-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-04-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL22183.068.08
Other	NTR1402 (Nederlands Trial Register)