Dyspnoea in Pulmonary Arterial Hypertension: Targeting the Diaphragm muscle

Published: 29-07-2011
Last updated: 27-04-2024

PRIMARY OBJECTIVE:To determine the contractile strength and the (ultra)structure of single diaphragm muscle fibers of CTEPH patients SECONDARY OBJECTIVES:1. To determine whether diaphragm muscle fiber weakness is part of a generalized muscle...

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

Summary

ID

NL-OMON36056

Source
ToetsingOnline

Brief title
Diaphragm dysfunction in PAH

Condition

- Other condition
- Muscle disorders
- Pulmonary vascular disorders

Synonym
Pulmonary arterial hypertension diaphragm dysfunction

Health condition

aandoeningen van de ademhalingsspieren

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Diaphragm, function, hyperventilation, pulmonary arterial hypertension

Outcome measures

Primary outcome

Main study parameter/endpoint: Contractile force and structure of single

diaphragm muscle fibers

Secondary outcome

Secondary study parameters/endpoints: * Morphological determination of muscle

fiber cross sectional area * Muscle fiber ultrastructure by electronmicrocopy *

Posttranslational modification of contractile proteins * Diaphragm cytokine

profile * Gene expression analysis by Affymetrix

* Comparison of findings from diaphragm muscle to those from the

non-respiratory pectoralils major muscle * Correlation between diaphragm muscle

fiber strength and pulmonary function

Study description

Background summary

Pulmonary arterial hypertension (PAH) is defined by an isolated increase in pulmonary vascular resistance and eventual right ventricular failure. Patients with PAH are severely limited in their daily-life activities because of dyspnoea; the sensation of dyspnoea is very uncomfortable and is an important factor limiting exercise tolerance in these patients. The mechanism underlying

dyspnoea in PAH are incompletely understood. We propose that the pathogenesis of this disorder is caused largely by weakening of the diaphragm muscle, the primary inspiratory muscle.

Evidence for our proposition has been provided by recent studies suggesting that the inspiratory muscles in PAH are (i) weakened, and (ii) subjected to increased activity. It was shown that inspiratory pressure generation is significantly impaired in PAH patients. For instance, volitionally assessed maximal inspiratory mouth pressures and non-volitionally assessed transdiaphragmatic pressures during bilateral anterior magnetic phrenic nerve stimulation were markedly lower in PAH patients compared with control subjects. The notion that the inspiratory muscles are more active in patients with PAH comes from the observation that patients with PAH hyperventilate during exercise, at rest, and even during sleep. This continuous and unrelenting hyperventilation places an increased demand on the inspiratory muscles. Thus, patients with PAH need to breath more with weaker inspiratory muscles. This apparent disbalance in the demand placed on the inspiratory muscles on the one hand and the capacity of the inspiratory muscles to generate pressure on the other hand is likely to be a major contributor to the sensation of dyspnoea in PAH.

Recent studies from our group support the notion of diaphragm weakness in PAH. First, the maximal force generating capacity of intact diaphragm strips was decreased by ~30% in rats with PAH compared to control rats. Interestingly, this diaphragm weakness was not part of a generalized muscle weakness, as the force generating capacity of the extensor digitorum longus muscle was preserved in PAH rats. Secondly, post-mortem analysis of diaphragm structure in PAH patients revealed significant muscle fiber atrophy, with no change in quadriceps muscle. However, it is unclear whether this specific diaphragm fiber atrophy is found only in end-stage PAH or is also present in ambulatory PAH patients. Thus, whereas the evidence for diaphragm weakness in animal models is accumulating, the evidence for its occurrence in patients is lacking. The few studies directed at testing the presence of diaphragm weakness in PAH patients indicated that twitch transdiaphragmatic pressure obtained via magnetic phrenic-nerve stimulation was reduced; however, such reduction of twitch pressure might very well involve phenomena that reside outside the diaphragm. In this observational study, we propose to determine conclusively whether diaphragm weakness occurs in patients with PAH. To this end, studies on diaphragm muscle biopsies are indispensable: these will allow to study directly the contractile strength of isolated muscle fibers as well as the muscle fiber structure and the gene/protein expression profiles. The diaphragm biopsies will be obtained during pulmonary thrombo endarterectomy (PTE) of chronic thromboembolic pulmonary hypertension (CTEPH) patients. Thus, these biopsies will position us uniquely to determine, for the first time, the effect of PAH on diaphragm fiber contractile performance

Our study may provide rationale for the development of novel therapeutic strategies aimed to modulate the respiratory frequency to reduce the overload on the respiratory muscles, and thus also the sensation of dyspnoea in PAH

patients.

Study objective

PRIMARY OBJECTIVE:To determine the contractile strength and the (ultra)structure of single diaphragm muscle fibers of CTEPH patients
SECONDARY OBJECTIVES:1. To determine whether diaphragm muscle fiber weakness is part of a generalized muscle weakness, or rather is specific to the diaphragm muscle.2. To determine whether diaphragm muscle fiber strength correlates with pulmonary function
Note, that if these studies indicate diaphragm muscle fiber weakness in CTEPH patients, novel therapeutic strategies aimed to reduce the respiratory frequency, e.g. *-blockers, can be studied.

Study design

STUDY DESIGN * Prospective, observational study. * The study will be performed in the AMC in Amsterdam.
STUDY PERIOD * The study will end when the required population size for the CTEPH patients is reached. FLOW CHART CTEPH patients * Designated pulmonology physicians at AMC and VUMC will identify eligible CTEPH patients who are planned for a pulmonary thrombo endarterectomy (PTE) (~15 per year). * In case the patient agrees with the biopsy procedure, the informed consent form is signed. * Surgery: during PTE, the surgeon obtains a small biopsy (~50 mg) from the diaphragm muscle at the end of the PTE procedure at the mid-costal region of the diaphragm. Moreover, a small biopsy from the pectoralis major muscle will be obtained; this muscle will be readily accessible due to the already existing incision through the sternum (note that the pectoralis major biopsy will allow to compare the findings obtained from the diaphragm to those from a non-respiratory muscle). The surgical procedure will be attended by the coordinating investigator or by a trained co-investigator for adequate storage of tissue and for subsequent transportation to the Laboratory for Physiology at VUmc. * The majority of the experiments on the biopsies will be performed at the Laboratory for Physiology at VUmc.

Study burden and risks

The diaphragm (and pectoralis major) biopsy is very small (~50mg) and will induce only very little and reversible damage. Previous studies performed by the principal investigator (CAC Ottenheijm) at the Radboud University Nijmegen Medical Centre (dept. of Pulmonary diseases) using diaphragm biopsies obtained by comparable procedures as described here, were completed without any adverse events(~200 biopsies). Furthermore, an evaluation of the pain experienced after surgery by patients from whom a diaphragm biopsy was obtained (n=30) revealed that these patients did not observe more pain than patients (n=40) from whom no biopsy was obtained. The principal investigator (CAC Ottenheijm) was involved

in this evaluation, which was performed at the Radboud University Nijmegen Medical Centre (dept of Pulmonary Diseases) in 2001. Thus, we are confident that the risk for the patients are negligible and that the burden can be considered minimal (patients are already scheduled for, and the biopsy collection will not significantly delay the duration of, the surgery; the average duration required for biopsy collection by the surgeon is one minute). Importantly, the knowledge obtained by experiments on these valuable biopsies will provide extremely precious insights into the role of diaphragm weakness in pulmonary hypertension. This knowledge can subsequently be used for novel treatment strategies to prevent diaphragm muscle weakness in pulmonary hypertension patients.
The proposed research can be regarded group-related, as the participation of subjects belonging to the group in question is indispensable. These patients have CTEPH for years and the pulmonary function can be tested profoundly; such research is technically and financially not feasible in laboratory animals.

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

- Patients with chronic thromboembolic pulmonary hypertension scheduled for a pulmonary thrombo endarterectomy.
- Age: > 18 years
- Gender: Both male and female
- all ethnic backgrounds

Exclusion criteria

- COPD (GOLD stage II-IV) and CHF (NYHA class III-IV)
- Neuromuscular disease
- chronic use of corticosteroids (defined as >7.5 mg/day for at least 3 months)
- >10% weight loss within last 6 months

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2011
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL35733.018.11