Ventilator-Induced Diaphragm Dysfunction in ICU patients

Published: 27-05-2010
Last updated: 04-05-2024

PRIMARY OBJECTIVE1. To determine the contractile strength and the (ultra)structure of single diaphragm muscle fibers of mechanically ventilated patientsSECONDARY OBJECTIVE1. To determine whether diaphragm muscle fiber weakness is part of a...

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

Summary

ID

NL-OMON44050

Source
ToetsingOnline

Brief title
Diaphragm weakness in the ICU

Condition

- Other condition
- Muscle disorders

Synonym
ventilator-induced diaphragm dysfunction (VIDD)

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, sepsis, ventilation

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 rectus abdominus muscle and latissimus dorsi.

•Correlation between diaphragm muscle fiber strength and the number of failed weaning trials.

•Effect of duration of mechanical ventilation on contractile strength (by comparing individuals with various durations of mechanical ventilation).

•Microvascular function.

•Inflammation

Study description

Background summary

Severe sepsis, trauma, abdominal haemorrhage and vascular injury are the leading cause of mortality in the intensive care unit (5). Current treatment modalities include the early institution of ventilation support, mainly to support gas exchange. However, mechanical ventilation is clearly a two-edged sword: a rapidly accumulating body of evidence suggests that mechanical ventilation, with its attendant diaphragm muscle inactivity, is an important cause of diaphragmatic weakness. Thus, after surviving the perils of sepsis, trauma, abdominal haemorrhage and vascular injury, continued mechanical ventilation may be required because of profound diaphragm weakness, leading to difficulties in discontinuing ventilatory support (i.e. weaning failure). Weaning failure is frequently encountered and a major clinical problem in mechanically ventilated patients (1) and contributes to mortality (3).

How does prolonged mechanical ventilation weaken the human diaphragm? The plethora of data suggesting that the ventilator causes damage to the diaphragm are from animal studies. In rats, two days of controlled mechanical ventilation reduced the pressure-generating capacity of the diaphragm by nearly fifty percent (2). This decrease in diaphragmatic force is time-dependent, becoming evident as early as twelve hours after onset of mechanical ventilation in rats (15) and worsens as this ventilation is prolonged (16), and appears to be specific for the diaphragm. This so-called ventilator-induced diaphragmatic dysfunction (VIDD) is mainly caused by rapid atrophy of the diaphragm, in which oxidative stress appears to play a key role (17) together with other factors such as steroid (mis)use, malnutrition, hyperglycemia, and the type of ventilatory support.

Whereas the evidence for VIDD in animal models is strong, this evidence for its occurence in patients is lacking. The few studies directed at testing the presence of VIDD in patients indicated that twitch transdiaphragmatic pressure obtained via magnetic phrenic-nerve stimulation was reduced in mechanically ventilated patients(4); however, such reduction of twitch pressure might very well involve phenomena that reside outside the diaphragm.

In this observational study, we propose to determine whether VIDD occurs in patients. 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 laparotomy or thoracotomy performed on mechanically-ventilated patients for suspected or proven intra-abdominal sepsis or trauma, abdominal haemorrhage, or patients scheduled for vascular surgery. Thus, these biopsies will position us uniquely

to determine, for the first time, the effect of mechanical ventilation on diaphragm fiber contractile performance.

Our study may provide rationale for the development of novel therapeutic strategies aimed at preventing or treatment of diaphragm weakness (such as Neurally Adjusted Ventilatory Assist (NAVA) ventilation technology and/or calcium sensitizers), and ultimately weaning failure, in mechanically ventilated septic and non-septic patients in the ICU.

Study objective

PRIMARY OBJECTIVE
1. To determine the contractile strength and the (ultra)structure of single diaphragm muscle fibers of mechanically ventilated patients

SECONDARY OBJECTIVE
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 the duration of ventilatory support.
3. To determine whether diaphragm muscle fiber strength correlates with weaning failure.

Note, that if these studies indicate diaphragm muscle fiber weakness in mechanically ventilated septic and non-septic patients, future studies will test whether this can be attenuated by NAVA ventilation technology to avoid diaphragm disuse atrophy.

Study design

Study design:
•Prospective, observational study.
•The study will be performed in the VUmc in Amsterdam.

Study period:
•The study will end after 4 years or earlier when the required population size for the mechanically ventilated and control patients is reached.

Flow chart:
Mechanically ventilated septic patients planned for a laparotomy and non-septic patients planned for a laparotomy or thoracotomy for other reasons such as trauma, abdominal haemorrhage, vascular surgery
•Designated ICU physicians (surgeons, intensivists, anaesthesiologists) at VUmc or MST will identify eligible mechanically-ventilated septic and non-septic patients who are planned for a laparotomy or thoracotomy for suspected or proven intra-abdominal sepsis (~50 per year), abdominal haemorrhage, or patient

that need vascular surgery.
•As the majority of these patients is incapacitated, the patient*s respresentative(s) will be contacted by the physician responsible for recruitment.
•In case the representative agrees with the biopsy procedure, the informed consent form is signed.
•Surgery: during the laparotomy or thoracotomoy, the surgeon obtains a small biopsy (~50 mg) from the diaphragm muscle. Moreover, a small biopsy from the rectus abdominus muscle or latissimus dorsi muscle will be obtained; this muscle will be readily accessible due to the already existing incision (note that the rectus abdominus 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. Directly prior to the biopsy, sidestream dark field imaging will be applied. The imaging takes place by means of a sterile probe, with the size of a pen, and which will be placed gently against the diaphragm via the already existing incision. The imaging procedure is performed by well-trained researchers/physicians. The application of the imaging is non-invasive and extends the surgery by ~1 minute.
•As soon as the patient regains consciousness, the patient will be informed about the study, and will be asked for informed consent.
•The majority of the experiments on the biopsies will be performed at the Laboratory for Physiology at VUmc.

Non-mechanically ventilated non-septic patients (these will serve as controls):
•The designated thoracic surgeon at VUmc will identify eligible patients who are planned for a thoracotomy for removal of a small tumor (~30 per year).
•In case the patient agrees with the biopsy procedure, the patient will sign the informed consent form prior to surgery.
•Surgery: during the thoracotomy, the surgeon obtains a small biopsy (~50 mg) from the diaphragm muscle. Moreover, during surgery the surgeon will take a small biopsy from the latissimus dorsi. 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 rectus abdominal and latissimus dorsi) biopsy is very small (~50 mg) and will induce only very little and reversible damage. Previous studies performed by the coordinating 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, obtained from Radboud

University Nijmegen Medical Centre, Rijnstate Hospital, and Catharina Hospital).

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 coordinating investigator (CAC Ottenheijm) was involved in this evaluation, which was performed at the Radboud University Nijmegen Medical Centre (dept of Pulmonary Diseases) in 2001.

The sidestream dark field imaging takes place by means of a sterile probe, with the size of a pen, and which will be placed gently against the diaphragm via the already existing incision. The imaging procedure is performed by well-trained researchers/physicians, is non-invasive and extends the surgery by ~1 minute.

Thus, we are confident that the risk for the patients are negligible and that the burden can be considerd minimal (patients are already scheduled for, and the biopsy collection/imaging procedure will not significantly delay the duration of, the surgery; the average duration required for biopsy collection/imaging procedure by the surgeon is one-two minutes). Importantly, the knowledge obtained by experiments on these valuable biopsies and by the imaging will provide extremely precious insights into the role of diaphragm weakness in weaning failure in the ICU. This knowledge can subsequently be used for novel treatment strategies to prevent diaphragm muscle weakness in mechanically-ventilated septic and non-septic patients.

The proposed research can be regarded group-related, as the participation of subjects belonging to the group in question is indispensable. Many of these patients are mechanically ventilated for weeks/months; 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

-Mechanically ventilated septic patients in the ICU planned for a laparotomy for suspected or proven intra-abdominal sepsis (incidence: ~50 p year), and mechanically ventilated non-septic patients in the ICU planned for a laparotomy or thoracotomy for other reasons such as trauma, abdominal haemorrhage, vascular surgery and patients scheduled for a thoracotomy for removal of a small (T1-T2) pulmonary tumor (these will serve as control subjects).
-Age: >18 years
-Gender: both male and female
-all ethnic backgrounds

Exclusion criteria

-COPD (GOLD stage II-IV) or CHF (NYHA class III-IV)
-Neuromuscular disease
-Drugs known to alter muscle structure and function
-Chronic metabolic disease
-Pulmonary hypertension
-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
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2010
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO Date:	27-05-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2016
Application type:	Amendment
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	NL31909.029.10