ICU-Acquired Respiratory muscle Dysfunction (the ICARD study)

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Primary: To determine the contractile strength and the structure of single muscle fibers isolated from biopsies of the diaphragm and lateral abdominal muscles from mechanically-ventilated patients. Secondary: (i)To elucidate the molecular mechanisms...

Ethical review	Approved WMO
Status	Pending
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON51396

Source
ToetsingOnline

Brief title
ICARD

Condition

- Muscle disorders

Synonym
Diaphragm muscle weakness, Expiratory muscle weakness, Ventilator induced expiratory muscle dysfunction, Ventilator-induced diaphragm dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ZonMW open;dossiernummer 09120011910004

Intervention

Keyword: Intensive care, Mechanical ventilation, Respiratory muscle dysfunction

Outcome measures

Primary outcome

Contractile force of single respiratory muscle fibers.

Secondary outcome

Morphological determination of muscle fiber cross sectional area

Muscle fiber ultrastructure by electronmicrocopy

Muscle fiber nuclear shape and function

Posttranslational modification of contractile proteins

Diaphragm cytokine profile

Plasma cytokine profile

Gene expression analysis by RNA-sequencing

Comparison of findings from diaphragm muscle to those from the non-respiratory rectus abdominus muscle (and latissimus dorsi in the control group).

Comparison of findings from diaphragm and rectus abdominus muscle (latissimus dorsi in the control group) to expiratory respiratory muscles (lateral abdominal muscles in the ICU group and in control group).

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

Microvascular function

Inflammation

Diaphragm and expiratory muscle thickness, echogenicity and layering determined

by bedside ultrasound.

Study description

Background summary

Severe sepsis, trauma, abdominal haemorrhage and vascular defects are the leading causes of mortality in the intensive care unit. 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 inactivity of the respiratory muscle pump, is an important cause of respiratory muscle weakness. This so-called ventilator-induced respiratory muscle dysfunction is mainly caused by rapid atrophy. Thus, after overcoming the perils of critical illness, continued mechanical ventilation may be required because of profound respiratory muscle weakness, leading to difficulties in discontinuing this ventilatory support (i.e. weaning failure). Weaning failure is frequently encountered in mechanically ventilated patients and contributes to mortality.

In our previous study that focused on the diaphragm, a profound effect of mechanical ventilation was found. Diaphragm muscle fibers of mechanically ventilated patients had a reduced cross-sectional area and lower normalized force. These findings warrant further investigation into the underlying molecular mechanisms to identify targets for pharmacological intervention.

The lateral abdominal wall muscles (expiratory muscles) are recruited with active expiration during high breathing effort or inspiratory muscle weakness. The effects of critical illness and mechanical ventilation on these muscles has been assessed by bedside ultrasound. Changes in thickness occurred in 34 percent of patients. No data is available on histology and contractility of the lateral abdominal muscles of critically ill patients.

In this observational study, we propose to elucidate the pathophysiology of diaphragm weakness in critically ill patients and include in our evaluation the role of the main components of the respiratory pump other than the diaphragm .

Study objective

Primary: To determine the contractile strength and the structure of single muscle fibers isolated from biopsies of the diaphragm and lateral abdominal muscles from mechanically-ventilated patients. Secondary: (i)To elucidate the molecular mechanisms underlying ventilator-associated diaphragm dysfunction.

(ii) To determine whether respiratory muscle fiber weakness is part of a generalized muscle weakness, or rather is specific to the respiratory muscles and (iii) to determine the relationship between contractile properties of single muscle fibers on one hand, and respiratory muscle thickness and echogenicity as measured with ultrasound on the other hand.

Study design

Designated ICU physicians (surgeons, intensivists, anesthesiologists) at participating centers will identify eligible mechanically-ventilated patients who are planned for a laparotomy (~50 per year), or thoracotomy. As these patients are incapacitated, the patient*s representative(s) will be contacted by the responsible physician for possible recruitment. In case the representative agrees with the study procedures, the informed consent form is signed. At one point of time during the 24 hours before the surgery, 3 ml of blood is collected. Diaphragm and expiratory muscle thickness, echogenicity and layering are measured by an experienced physician or researcher using bedside ultrasound.
Surgery: during the laparotomy or thoracotomy, the surgeon obtains a small biopsy (~50 mg) from the diaphragm muscle. Moreover, a small biopsy from the rectus abdominis and lateral abdominal muscles will be obtained; these muscles will be readily accessible due to the already existing incision through the abdominal wall (note that the rectus abdominis 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 Amsterdam UMC, location VUmc. The majority of the experiments on the biopsies will be performed at the Laboratory for Physiology at VUmc.

For the collection of the muscle biopsies from non-mechanically ventilated patients (these will serve as controls), patients scheduled for thoracotomy for removal of a small pulmonary tumor will be recruited by the thoracic surgeon. Patients scheduled for abdominal surgery will be recruited by the abdominal surgeon. The flow chart is comparable to that for critically ill mechanically ventilated patients shown above, with the exception that these patients are capacitated and will provide informed consent themselves, prior to surgery. Additionally, in the thoracotomy group, the non-respiratory latissimus dorsi muscle will be biopsied as this tissue is easily accessible through the existing incision. In the abdominal surgery control group the surgeon will take a small biopsy from the lateral abdominal muscles and the rectus abdominal muscle through the existing incision the surgeon made to access the abdomen. In this group, no diaphragm biopsy will be taken.

Study burden and risks

In the mechanically ventilated (ICU) group the burden associated with participation consists of (1) the collection of a small (~50 mg) diaphragm biopsy, (2) the collection of a biopsy of the lateral abdominal wall muscles, (3) the collection of a biopsy from the rectus abdominis muscle ,(4) the employment of bedside ultrasound to obtain insight in diaphragm and expiratory muscle thickness, echogenicity and layering and (5) the collection of 3ml of blood before the surgery. In the first control group the burden associated with participation consists of (1) the collection of a small (~50 mg) diaphragm biopsy, (2) the collection of a biopsy of the latissimus dorsi (LD) muscle, (3) the employment of bedside ultrasound to obtain insight in diaphragm and expiratory muscle thickness, echogenicity and layering and (4) the collection of 3ml of blood before the surgery. In the abdominal surgery control group the burden consists of (1) a small biopsy of the lateral abdominal muscles, (2) a small biopsy of the rectus abdominis muscle and (3) the employment of bedside ultrasound to obtain insight in expiratory muscle thickness, echogenicity and layering and (4) the collection of 3 ml of blood before the surgery.
There will be no benefit for the subjects.

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

1. mechanically ventilated patients planned for a laparotomy for suspected or proven intra-abdominal sepsis or for other reasons such as trauma, abdominal haemorrhage, vascular surgery. (50 patients)
2. Patients scheduled for elective thoracotomy or lobectomy for removal of a pulmonary tumor (30 patients).
3. Patients scheduled for elective abdominal surgery (30 patients)

-Age: >18 years
-Informed consent

Exclusion criteria

COPD (GOLD 3-4) or CHF (NYHA 3-4)
-Neuromuscular disease
-Chronic metabolic disease
-Pulmonary hypertension
-Chronic use of corticosteroids (defined as >7.5 mg/day for at least 3 months)
-Drugs known to alter muscle structure and function
->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:	Pending
Start date (anticipated):	01-04-2022
Enrollment:	110
Type:	Anticipated

Ethics review

Approved WMO

Date:	17-08-2022
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	NL80196.029.22