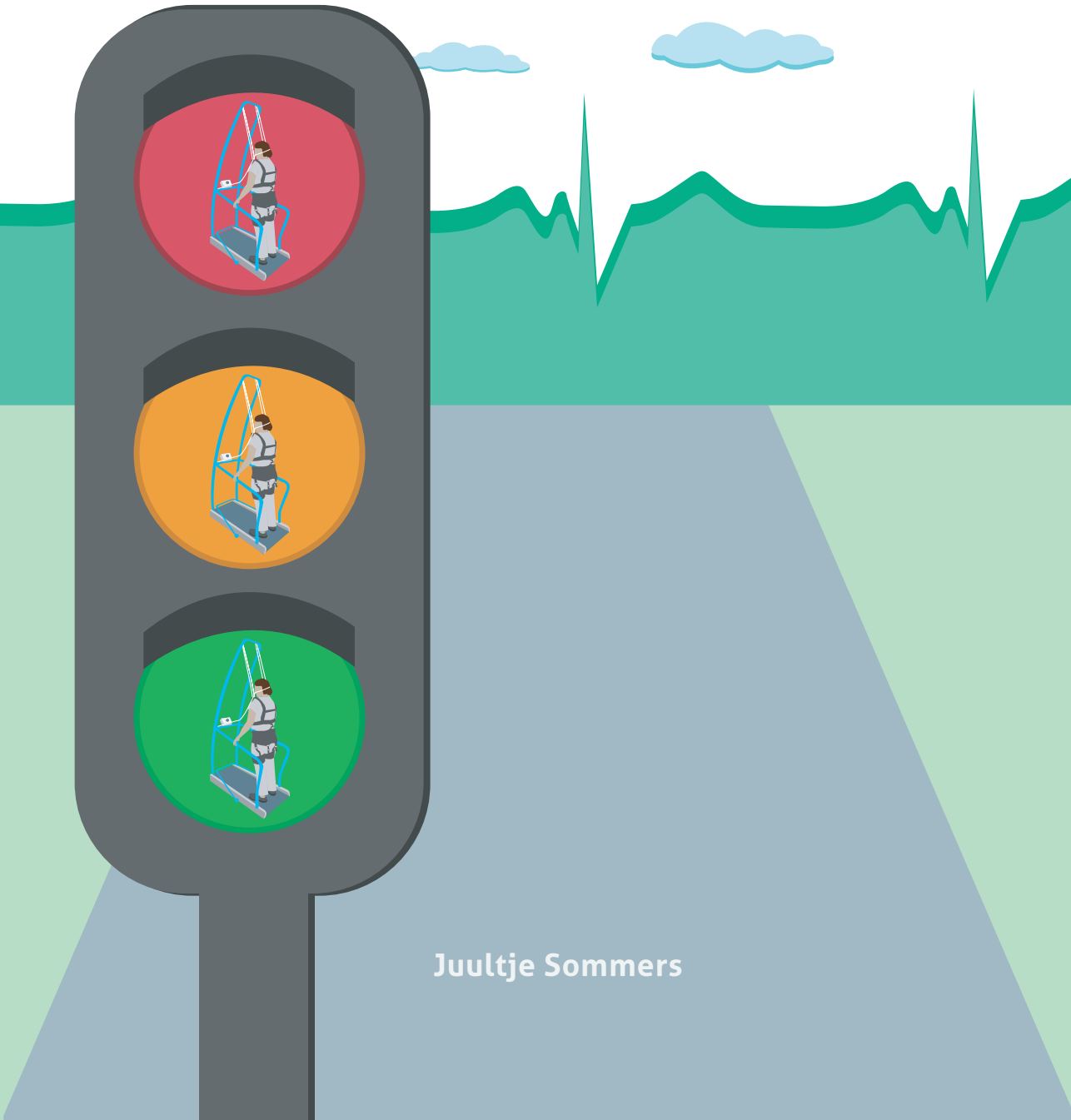
PHYSICAL THERAPY FOR PATIENTS IN THE INTENSIVE CARE UNIT

Towards safe and purposeful physical therapy practice for critically ill patients



Juultje Sommers

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Thesis University of Amsterdam, The Netherlands

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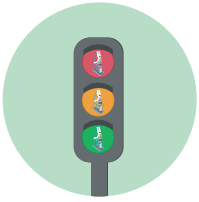
CONTENTS

CHAPTER 1

General introduction



Each year about 85.000 patients with various life-threatening conditions are admitted to an intensive care unit (ICU) in the Netherlands (1). Due to improvements in medical care, the survival rate of these critically ill patients has significantly increased over the past decennia (2-4). Consequently, an increasing number of patients survive an ICU stay with long-term residual symptoms and restrictions in daily functioning and decreased quality of life (3). In 2012, the Society of Critical Care Medicine introduced the term "Post-Intensive Care Syndrome"(PICS) to describe the physical, mental, and cognitive impairments arising after critical illness (see fig 1) (5). The term can be applied to a survivor (PICS) or family member (PICS-F) (5). Risk factors for PICS are age, comorbidity burden, the severity of illness and the (duration of) ICU treatment (6-8). Although the exact prevalence of PICS among ICU survivors is unknown, it is estimated that 20-25% of patients will suffer from some component of PICS after ICU and hospital discharge (9, 10).

In the Netherlands, yearly approximately 20.000 ICU survivors are discharged from the ICU with symptoms of PICS (11).

In this thesis, particular the physical impairments from the PICS framework in relation with physical therapy in the ICU, will be highlighted.

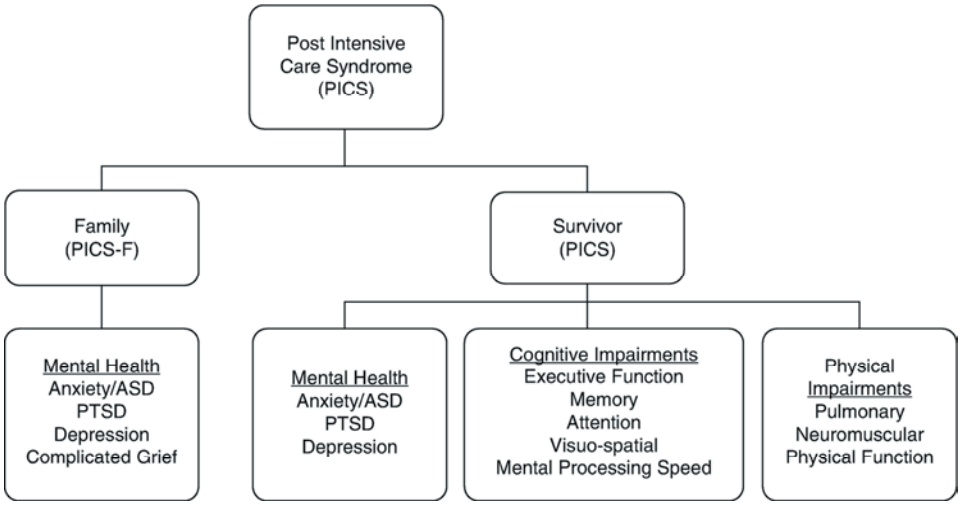


Figure 1 Post intensive care syndrome (PICS) conceptual diagram (5)
Abbreviations: ASD: acute stress disorder; PTSD: posttraumatic stress disorder

The severity of physical impairments is to a great extent associated with the severity of the critical illness leading to the ICU admission (12-14). Moreover, the presence of sepsis induces a systemic inflammatory response which can affect multiple organs leading to Multiple Organ Failure (MOF) (15). Besides the failure of vital organs such as heart, lungs

and kidneys, MOF can also involve the neuro-musculoskeletal system (see fig 2) (14, 16-18). Generalized muscle weakness, usually denominated as intensive care unit-acquired weakness (ICU-AW), is one of the most commonly observed physical impairments of critical illness (16, 18-22). ICU-AW is caused by dysfunction or damage of the muscles (critical illness myopathy), nerves (critical illness neuropathy), or both (critical illness neuromyopathy) (22). ICU-AW involves the muscles of the trunk, lower and upper extremities as well as the respiratory muscles. The facial muscles often remain unaffected (22). ICU-AW is diagnosed by manual testing of muscle strength with Medical Research Council sum score of < 48 indicating ICU-AW (22). ICU-AW is associated with a longer duration of mechanical ventilation, longer ICU and hospital stay, increased mortality, delayed rehabilitation and reduced quality of life (22-27). In addition to the severity of illness, the necessary treatment and the duration of the critical illness influence physical functioning (which refers to the practical application using whole-body integration of the cardiovascular-, respiratory- and/ or neuro musculoskeletal system (see fig.2)), particularly the resulting bedrest and inactivity (28). Because of the critical medical situation, patients in an ICU are attached to supportive medical devices such as, mechanical ventilation, renal replacement therapy, drains and infusions. These devices impede physical activity. Also sedative medication in the acute phase of the critical illness contributes to inactivity and bedrest. Bedrest negatively adds to the decline in physical functioning it eliminates the influence of gravity and has detrimental influence on metabolism and muscle protein synthesis (29). Also inactivity results in a decrease of muscle contractions and a reduction in the cardiovascular- and respiratory condition (26).

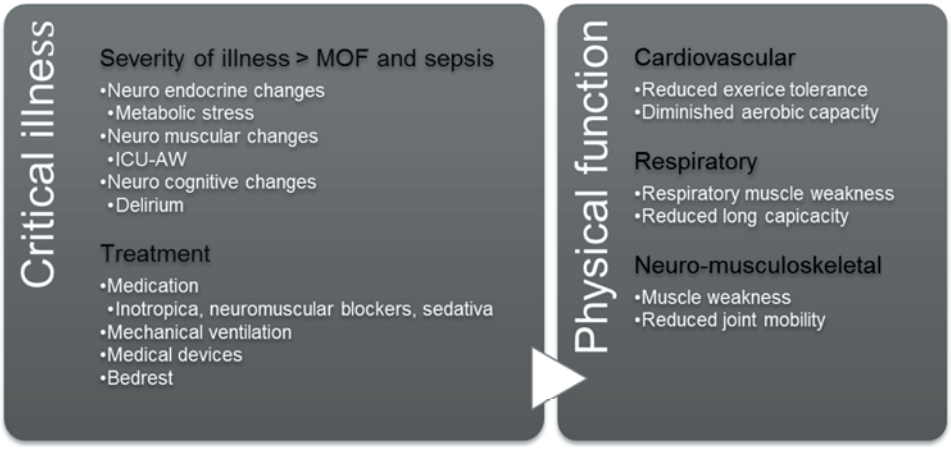


Figure 2 Impact of critical illness at physical impairments

Abbreviations: MOF: Multiple Organ Failure; ICU-AW: intensive care unit-acquired weakness

PHYSICAL THERAPY FOR PATIENTS IN THE ICU

Physical therapy consists of services provided by physical therapists to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan (30). In the ICU physical therapy aims to prevent physical impairments and to promote physical functioning. In the ICU, the physical therapist is an indispensable member of the multidisciplinary team, who aims to preserve or improve physical function with respect to among other, muscle strength, exercise tolerance and the performance of physical activities.

With physical impairments being predominantly contributing to PICS, it has been proposed to start as early as possible with physical therapy in the ICU (31, 32). Several studies showed the positive effects of physical therapy interventions (such as cycling, physical exercises, mobilization in and out of the bed and ambulation) on muscle strength, physical functioning and quality of life as well as, delirium, the duration of mechanical ventilation, length of ICU and hospital stay (12, 23, 31, 33-41). The effects of physical therapy treatment strategies on different aspects of functioning and disabilities can be measured and classified according to the domains of the International Classification of Functioning, Disability and Health (ICF) (42-44). The ICF framework consists of 3 core domains to describe the level of functioning: (1) body functions and structures, (2) activities, and (3) participation (44, 45). The ICF has a logical coherent content, aids in determining classification and effective decision-making, measuring outcomes and is adopted in medical rehabilitation and physical therapy (figure 3).

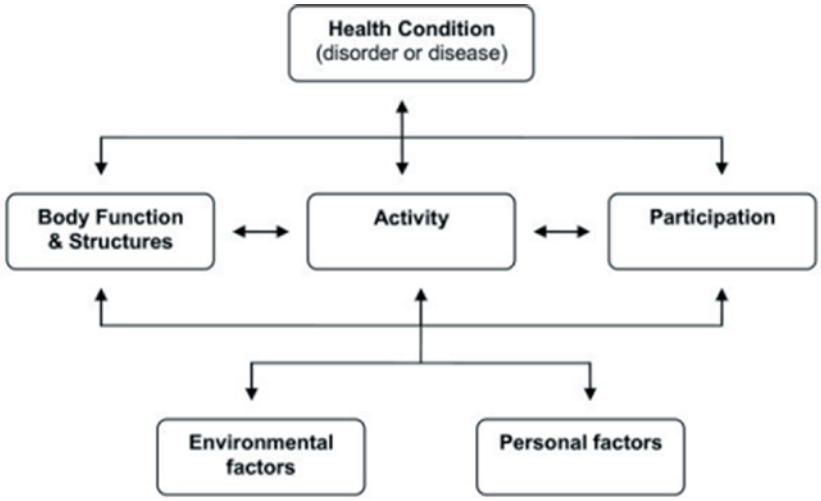


Figure 3 International Classification of Functioning, disability and health (44)

To implement physical therapy in an ICU setting, safe treatment strategies and accurate assessment of physical functioning based on the ICF framework are required. Because physical therapy goals differ between the different phases of recovery aiming at different domains of body functions and structures (muscle atrophy, strength and exercise capacity) and activities (transfers and walking capacity).

Although the different physical therapy interventions are applied in daily clinical practice in the ICU, questions remain regarding the optimum dosage and intensity (31, 32). Moreover, in order to improve physical functioning, the training load should be sufficient with respect to the training load principles of the Academy of Sport Sciences, the Frequency, Intensity, Time and Type parameters (FITT parameters) (46). At the same time, exercise should be safe and physiological overload should be avoided in ICU patients. At present, consensus about the safety and diagnostic process of physical therapy interventions and knowledge on the physiological response to exercise of patients with severe illness is scarce (31). Therefore, it is unknown, when to start safely with physical therapy and how to determine the optimal training load (31, 32, 34, 35, 47, 48). At present, a scientific basis for exercise prescription is lacking and physical therapists have to take a pragmatic approach to the rehabilitation. Therefore it is important to explore the physiological response to exercise of ICU patients and whether it is possible to measure this response. Furthermore, it is of vital importance that guidelines or evidence statements regarding the safety criteria for patients in the ICU are being developed, so patients' safety can be monitored during exercise.

Theoretically, early rehabilitation is initiated as soon as possible (34, 49-52). However, in clinical practice, in addition to safety issues, there are several practical barriers for the implementation of physical therapy for critically ill patients in the ICU. Recent literature reports lack of staff and time, potential risks of airway dislodgement and dislocation of intravenous and arterial lines, and monitoring as common barriers for early rehabilitation in the ICU (38, 49, 53, 54).

OUTLINE OF THE THESIS

In this thesis several aspects of physical therapy on the ICU were investigated. First, we developed recommendations for safe and purposeful physical therapy in patients in the ICU. Secondly, we investigated the physiological response and methods to assess changes in this response during bed cycling exercise. This was done in several pilot studies. Finally, the safety and feasibility of a new method of early rehabilitation focused on walking was explored.

Chapter 2 describes evidence-based recommendations for ICU physical therapy consisting of safety criteria, measurement instruments to assess physical function and

treatment strategies within the ICF framework, based on a review of the literature and consensus.

The study in **chapter 3** describes the evaluation of the feasibility, reliability and validity of measurement instrument to evaluate mobility in critically ill patients: the “de Morton Mobility Index (DEMMI)”.

The next two chapters contain studies that explore the response to exercise in critically ill patients. In **chapter 4** the safety and physiological response to incremental exercise using a bedcycle ergometer is investigated. In **chapter 5** the changes in electrical activity of the m. quadriceps by surface electromyography (sEMG) during bed cycling is described.

Chapter 6 describes the feasibility of early ambulation training with a body weight supporting treadmill that we developed for the use in critically ill patients in the ICU.

The thesis is concluded with a general discussion in **chapter 7** which summarizes the main findings and limitations of this thesis. Also recommendations for optimal care for physical therapy in the ICU and for future research are provided.

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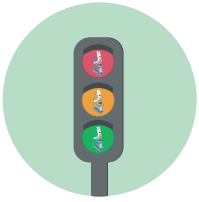
CHAPTER 2

Physiotherapy in the intensive care unit:an evidence-based, expert driven, practical statement and rehabilitation recommendations

Juultje Sommers, Raoul H.H. Engelbert, Daniela Dettling-Ihnenfeldt, Rik Gosselink, Peter E. Spronk, Frans Nollet, Marike van der Schaaf



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ABSTRACT

Objective: To develop evidence-based recommendations for effective and safe diagnostic assessment and intervention strategies for the physiotherapy treatment of patients in intensive care units.

Methods: We used the EBRO method, as recommended by the 'Dutch Evidence Based Guideline Development Platform' to develop an 'evidence statement for physiotherapy in the intensive care unit'. This method consists of the identification of clinically relevant questions, followed by a systematic literature search, and summary of the evidence with final recommendations being moderated by feedback from experts.

Results: Three relevant clinical domains were identified by experts: criteria to initiate treatment; measures to assess patients; evidence for effectiveness of treatments. In a systematic literature search, 129 relevant studies were identified and assessed for methodological quality and classified according to the level of evidence. The final evidence statement consisted of recommendations on eight absolute and four relative contra-indications to mobilization; a core set of nine specific instruments to assess impairments and activity restrictions; and six passive and four active effective interventions, with advice on (a) physiological measures to observe during treatment (with stopping criteria) and (b) what to record after the treatment.

Conclusions: These recommendations form a protocol for treating people in an intensive care unit, based on best available evidence in mid-2014.

INTRODUCTION

More than 75000 patients with various life-threatening conditions are admitted to a Dutch intensive care unit each year.(1) Although the survival rate of these seriously ill patients has significantly increased through improvements in medical care, the number of patients with long-term impairments, regardless of the medical diagnosis of admission to the intensive care unit, has also increased.(2) Critical illness oftentimes associated with long-term bed rest and inactivity may lead to intensive care unit-acquired muscle weakness.(3)

Intensive care unit-acquired muscle weakness is strongly associated with increased short- and long-term morbidity, physical impairments and mortality.(4) Intensive care unit-acquired muscle weakness is a frequently observed complication of critical illness, occurring in approximately 50% of intensive care patients.(3,4) Growing evidence exists that early physiotherapy interventions (mobilization and stimulation of activities) in critically ill intensive care patients may influence or even prevent physical impairments. (5–12) Within this literature, consensus about the use of physiotherapeutic measurement tools and strategies concerning the musculoskeletal and cardiopulmonary system are lacking.(11)

Moreover, with the recognition of the importance of early mobilization of critically ill patients, a clear description of the physiotherapy clinical practice within the intensive care multidisciplinary team is warranted. Also guidelines or evidence statements regarding the safety and diagnostic process of physiotherapy interventions in intensive care patients, as well as the effectiveness of these interventions are needed.(13,14)

The effects of physiotherapeutic treatment strategies on different aspects of functioning and disabilities can be measured and classified according to the domains of the International Classification of Functioning, Disability and Health (ICF).(15,16) The ICF has a logical coherent content, aids in determining classification and effective decision-making and is adopted in rehabilitation service. The purpose of this work was to formulate an evidence-based, expert driven, practical statement within the ICF domains, regarding diagnostics and effective and safe physiotherapy treatment strategies aiming at early mobilization and physical activity for patients in an intensive care unit.

METHODS

For the development of an ‘evidence-based, expert driven, practical statement for physiotherapy in the intensive care unit’, we adhered to the recommendations of the ‘Dutch Evidence Based Guideline Development Platform’ (EBRO method). (17,18) This method systematically follows several steps towards the development of an evidence-based guideline or statement.

First, analyse the problem to identify relevant 'clinical key questions'; second, systematic search and appraise the literature systematically; and third write and discuss the draft guideline with feedback from experts and eventually establish the final recommendations. The final recommendations in this systematic process regarding diagnostics and treatment strategies of the musculoskeletal and cardiorespiratory system in intensive care patients were classified according to the ICF.(19)

A project group was established with expertise from intensive care medicine, intensive care physiotherapy, guideline development and research to execute and monitor the process. The following steps of the method, according to the Dutch Evidence Based Guideline Development Platform, were undertaken.

Problem analysis to identify relevant 'clinical key questions'

A postal survey among 70 Dutch hospital intensive care physiotherapists was held to search for the gaps in evidence-based clinical decision making with respect to intensive care physiotherapy. The domain of the respiratory system was not considered specifically, because of the current Dutch situation in which physiotherapist are primarily involved in the management of deconditioning.

With this, the following relevant clinical key questions were identified.

1. Which criteria are recommended in order to mobilize and activate patients in an intensive care unit safely?
2. Which clinimetrics and their psychometric properties are recommended to quantify physical functions and activities in intensive care patients according to the ICF classification?
3. Which physiotherapy interventions are effective to improve physical functions and activities in intensive care unit patients?

Systematic literature search

To answer the clinical key questions, we performed a systematic literature review with the following search terms: intensive care units, critical illness, acquired weakness, rehabilitation, physiotherapy, exercise therapy, functional training, activity of daily living, motor activity, early mobilization. Therefore we searched the electronic databases PubMed, Cochrane, Embase, PEDro and CINAHL from 1995 till September 2014.

We included studies with participants older than 18 years of age who were admitted to an intensive care unit. Articles regarding patients with neurological conditions that existed prior to intensive care unit admission, such as stroke and spinal cord lesions, were excluded.

Quality assessment of included articles

We assessed and classified the methodological quality of the retrieved studies into the level of evidence and grading of scientific conclusions according to the criteria of the Dutch quality institute for Health Care who are based on the Oxford Centre for Evidence-Based Medicine (OCEBM).(18,20,21)

- Level A1: Systematic review.
- Level A2: Double blinded randomized controlled trial of good quality and size.
- Level B: Comparable research with not all characteristics of A2 (e.g. patient controlled and longitudinal cohort studies).
- Level C: Non-comparable research.
- Level D: Experts opinion.

Formulation of recommendations

To answer the three clinical key questions, we summarized the articles and formulated draft recommendations. In addition to the evidence-based conclusions from the literature, the project group added clinical relevant aspects, such as feasibility and costs, referred to as 'other considerations' to the initial recommendations.(18,20) Each individual recommendation was based on the combination of the scientific level of evidence of the literature and the clinical expertise.

- Level 1: Recommendation based on evidence of research of level A1 or at least two independent studies from level A2.
- Level 2: Recommendation based on one Level A2 study or at least two independent Level B studies.
- Level 3: Recommendation based one study from Level B or C.
- Level 4: Recommendation based on experts opinion.

Feedback from experts and formulation of final recommendations

Two different expert groups reviewed the draft recommendations in three different feedback rounds. One expert group consisted of two representative intensivists from the Dutch Society of Intensive Care (NVIC), employed at an academic and a general hospital. The other expert group consisted of 16 physiotherapists employed at academic and general hospitals with at least three years of experience within the treatment of intensive care unit patients.

In the first feedback round, experts provided their opinion with respect to the content, feasibility and implementation issues on a form composed for this purpose. The study group adjusted the recommendations according to the feedback, where-upon the final

recommendations were presented again for approval to the expert groups. Finally, the agreed recommendations were integrated in a physiotherapy clinical reasoning workflow and submitted for final approval to the expert groups.

RESULTS

Problem analysis to identify relevant 'clinical key questions'

The survey revealed the need for recommendations in three areas:

- to guide clinical practice with respect to safety criteria for early mobilization and activation;
- for clinimetrics with good psychometric properties; and
- for interventions (frequency, intensity, type and time: the FITT components) to improve the cardiorespiratory system and musculoskeletal system in intensive care unit patients.(22)

The systematic literature search from 1995 till September 2014 yielded 129 studies. Two authors (JS and MvdS) assessed the studies for methodological quality. Subsequently, JS extracted the articles to answer the three clinical key questions and formulate draft recommendations.

Criteria for treatment and safety

In intensive care unit patients, early mobilization and activation is complicated because of the critical pulmonary and haemodynamic condition necessitating medication and invasive equipment. In addition, owing to critical illness, this medical situation can rapidly change. Therefore monitoring patients' safety before and during mobilization and activation is of vital importance.

As part of the clinical reasoning process, every patient should be screened for the presence of red flags (contra-indications) and relative contra-indications to consider (potential) risks and benefits before and during every physiotherapy treatment session. These are shown in Figure 1. The strength of evidence of the recommendations for red flags is Level 1 and for 'relative contra-indications' Level 3 and 4 evidence.(5,10,23–33)

It is recommended to screen every patient on the presence of red flags (contra-indications) and relative contra-indications to consider (possible) risks and benefits before and during every physiotherapy treatment session.
The criteria mentioned below are (relative) contra-indications for mobilizations out of bed and physical activities of intensive care patients and have to be taken into consideration during the clinical reasoning process.
An intensivist needs to be consulted in case of a patient showing one of the following conditions before mobilization/physical activities.

Red Flags (level 1)

Heart rate

- Recent myocardial ischemia
- Heart rate < 40 and > 130 beats/min

Blood pressure

- Mean Arterial Pressure (MAP) < 60 mmHg and > 110 mmHg

Oxygen saturation

- ≤ 90%

Parameters of ventilation

- Fractional concentration of inspired oxygen (FiO_2) ≥ 0.6
- Positive End Expiratory Pressure (PEEP): ≥ 10 cm H_2O

Respiratory frequency

- Respiratory frequency > 40 breath/min

Level of consciousness of patient

- Richmond Agitation Sedation Scale (RASS) score: -4, -5, 3, 4

Doses inotropic

- High inotrope doses
    - Dopamine ≥ 10 mcg/kg/min
    - Nor/adrenaline ≥ 0,1 mcg/kg/min

Temperature

- ≥ 38.5°C
- ≤ 36°C

Relative contra-indications (level 3 and 4)

- Clinical View
    - Decreased level of awareness/consciousness
    - Sweating
    - Abnormal face color
    - Pain
    - Fatigue
- Unstable fractures
- Presence of lines that make mobilization unsafe.
- Neurological instability: Intra Cranial Pressure (ICP) ≥ 20 cmH_2O

Figure 1 Criteria for safety of treatment

It is recommended to use these clinimetrics when needed for evaluate impairments and activities restrictions within the ICF classification.

Assessment of the musculoskeletal system

- Edema, muscle atrophy, contractures, deformities, bed sores, decubitus, wounds

Assessment

Function

- Consciousness
  - Richmond Agitation Sedation Scale (RASS; level 1)
- Cooperation
  - Standardized Five Questions (S5Q) (level 4)
- Active and Passive limitations in Rang Of Motion (ROM)
  - Goniometry measuring ROM (level 4)
- Muscle strength
  - Medical Research Council (MRC) (sum) score (level 2)
  - Hand held dynamometer or hand grip strength (Jamar) if MRC score of 3 has been reached (level 2)
- Muscle tone
  - Modified Ashworth Scale (MAS) (level 4)
- Sensation
  - Modified Notthingham Sensory Assessment (NSA) (level 4)

Activities

- Transfers
  - de Morton Mobility Index (DEMMI) (level 4)
- Walking
  - de Morton Mobility Index (DEMMI) (level 4)
- Exertion
  - Borg (level4)

Figure 2 The recommended assessment tools

Recommended assessments

The recommended assessment tools are (Figure 2):

- Richmond Agitation Sedation Scale (RASS): Screening of global mental functions, i.e. patients responsiveness and consciousness (Level 1);
- Standardized Five Questions (S5Q): Assessing patients' ability to cooperate (Level 4);
- Goniometry: Measuring range of joint motion (ROM) (Level 4);
- Medical Research Council sum score (MRC): Measuring manually localized muscle strength as well as the summation of total muscle strength (Level 2);
- Hand Hand held dynamometry (HHD): Measuring localized muscle strength in muscles with MRC > 3 (Level 2);

- Modified Ashworth Scale (MAS): Assessing muscle tone (Level 4);
- Modified Nottingham Sensory Assessment (NSA): Evaluating sensory function (Level 4);
- De Morton Mobility Index (DEMMI): Measuring functional ability (e.g. transfers in and out of the bed, standing balance and walking (Level 4);
- The Borg Score: Monitoring exertion during exercise (in conscious patients) (Level 4).

These clinimetrics have moderate to good psychometric properties and can be used, when indicated, for diagnostics and tailor-made interventions at the bedside to evaluate impairments and activity restrictions within the ICF classification. The levels of recommendations are described in detail in Note 2 of the Appendix, available online.

Which physiotherapy interventions are effective?

The interventions that are recommended for intensive care patients, regardless of their medical diagnosis, are presented in the physiotherapy clinical reasoning regarding the therapeutic process and presented in Figure 3. The strength of the recommendations was between 1 and 4. In Note 3 of the Appendix (available online) a detailed description of the interventions as well as the level of evidence is provided. In Table 1, a summary of the different recommended interventions is presented.

For clinical practice, the recommended physiotherapy interventions are divided into interventions for patients who are able (active interventions) and who are not able to follow instructions (passive interventions), determined primarily by the level of consciousness. Changes in safety parameters should be monitored during each treatment session.

For unconscious patients the range of motion for joint contractures and muscle tone using passive joint movements should be monitored daily.(25,30,34– 36)

In patients who are at risk for, or already have, joint contractures, stretching, splinting (37) or passive movements using continuous passive motion (CPM) should be applied for 20 minutes daily.(36,38)

In addition, passive cycling (20 minutes), CPM (10,38,39) or electrical muscle stimulation (EMS) should be applied daily to stimulate muscle contractions.(6,40–48)

For patients who are conscious and able to follow instructions, active therapy modalities in a functional context are recommended. For the prevention of joint contractures and muscle tone a sequence of five active range of motion exercises are recommended daily. (7,25,30,37) To prevent muscle atrophy and improve muscle strength, active exercises (building up training referring to FITT components: frequency, intensity, type and time, repetitions from eight till ten and sets from one till three,(25,30,37,49,50) as well as 20 minutes of active cycling (10) are recommended.

To improve functional performance, mobilization in a functional context towards standing position and walking (from sitting on the edge of the bed towards sitting in the chair, and eventually walking, training of daily activities and active cycling (20 minutes per day) (7,10,25,30,37,38,49,51–55) is recommended.

During the intervention the safety parameters, as well as the level of awareness/ consciousness, should be monitored (Appendix, Note 5 and 7, available online). The intervention should be stopped according to the termination criteria (Appendix, Note 6, available online).

Non-responsive and non-cooperative patient

- RASS Score < -2 (level 2)
- S5Q < 3 (level 4)

Responsive and adequate patient

- RASS Score ≥ -2 (level 2)
- S5Q ≥ 3 (level 4)

Passive (Note 3)

- Passive Exercise (level 2)
  - Repetitions: 5 times/joint
  - Sets: 1
  - Frequency: Once daily
- Stretching (level 2)
  - Duration: 20 minutes
- Passive cycling (level 2)
  - Duration: 20 minutes
- EMS (level 1 and 2)
  - Duration: 60 minutes
  - Intensity: 45 Hz
  - Frequency: Daily
- CPM (level 2)
  - 3 x 3 hours daily
- Splinting (level 4)
  - Duration: 2 hours on and 2 hours off

Active (Note 3)

- Exercise Therapy (level 4)
  - Intensity: (level4)
    BORG 11 – 13
  - Duration: (level 4)
    Repetitions: 8-10
  - Sets:3 (level 4)
  - Frequency: 1 – 2 times daily (level 4)
  - Build up (level 4)
    Step 1: Increase duration
    - Increase repetitions to 10

    Step 2: Increase number of sets
    - From 1 set to 3 sets

    Step 3: Increase intensity
    - From BORG score 11 to 13

    Step 4: Increase frequency
    - From once daily to twice daily
- ADL training: Balance, standing, walking (level 3)
- Out of bed mobilization (level 2)
- Cycling (level 2)
  - Duration: 20 minutes
  - Build up: Build up interval training towards 20 minutes

Figure 3 Physiotherapy intervention

Abbreviations: RASS: Richmond Agitation Sedation Scale; S5Q: Standardized Five Questions; EMS: electro muscular stimulation; CPM: continuous passive motion.

Table 1 The effects of physiotherapeutic interventions on functional movement in intensive care patients according to the ICF classification

Intervention	Effect on level of anatomical features	Outcome measure	Author, year (Level of evidence)	Scientific level of conclusion
Mobilization in chair	↑ Respiratory frequency, ↑ oxygen saturation, ↑ respiratory reserve, ↑ heart rate, ↑ blood pressure/MAP, ↑,Ve, Vt, fr, Vt/T1	Respiratory and hemodynamic parameters and blood values	Genc, 2012 (B); Stiller, 2004 (C); Zafiropoulos, 2004 (C)	2 and 3
Exercise therapy (passive and active); training of ADL's (mobilization protocol)	↑ Il-10 anti-inflammatory cytokine	Blood values	Winkelman, 2012 (B)	2
CPM	Decreased loss of proteins ↑ Wet weight/magnesium DNA ↓ Il-6 inflammatory cytokine	Muscle biopsy, blood values	Griffths ,1995 (B); Amidei, 2013 (B)	2
Stretching	↑ ROM	Passive knee extension test	Reid 2004 (B)	2
EMS	↑ Muscle thickness, ↑micro circulation, ↑ oxygen consumption, ↑ reperfusion, ↓ muscle atrophy	Ultrasound, NIRS, outline upper limb (of the lower extremity)	Gruther, 2010 (A2); Gerovasili, 2009 (B); Meesen, 2010 (B); Angelopoulos 2013 (B); Hirose 2013 (B)	1 and 2
Intervention	**Effect on level of functioning**	**Outcome measure**	**Author, year (Level of evidence)**	**Scientific level of conclusion**
Mobilization in chair	↑ Vt ↑ Inspiratory and expiratory muscle strength	MIP, MEP, Vt	Chang, 2011 (B)	2
Immobilization	↑ Impairment in ROM	Measuring angles of ROM	Clavet, 2008 and 2011 (C)	3
(Stationary) cycling	↑ Strength in muscles quadriceps at hospital discharge	HHD- isometric quadriceps strength	Burtin, 2009 (B)	2
EMS	↑ Muscle strength (prevention CIPNM)	MRC sum score, handgrip strength	Karatzanos, 2012 (B); Routsi, 2010 (B); Rodrigues, 2012 (B); Parry, 2013 (A1); Williams, 2014 (A1)	1 and 2

Table 1 The effects of physiotherapeutic interventions on functional movement in intensive care patients according to the ICF classification *(Continued)*

Intervention	Effects on level of activity	Outcome measure	Author, year (Level of evidence)	Scientific level of conclusion
Exercise therapy (passive and active); training of ADL's	↑ ADL's at hospital discharge	Katz-ADL, BI, FIM	Schweickert, 2009 (A2); Chen, 2012 (B)	1 and 2
(Stationary) cycling	↑ ADL's at hospital discharge	6 MWT, SF36	Burtin, 2009 (B)	2
Intervention	**Other effects**	**Outcome measure**	**Author, year (Level of evidence)**	**Scientific level of conclusion**
Exercise therapy 20 min (passive and active) Training of ADL's (mobilization protocol)	↓ ICU, hospital LOS	LOS ICU, hospital	Morris, 2008 (C); Winkelman 2012 (B)	2 and 3
EMS	↓ Weaning time, ↓ ICU, hospital LOS	MRC (sum)score , LOS ICU, hospital	Routsi,2010 (B); Williams 2014 (A1)	1 and 2

6MWT: 6-minute walking test; ADL: activities of daily living; BI: Barthel Index; CIPNM: critical illness polyneuromyopathy; CPM: continuous passive motion; EMS: electro muscular stimulation; FIM: Functional Independence Measure; fr: respiratory rate; HHD: hand held dynamometer; ICU: intensive care unit; LOS: length of stay; MAP: mean arterial pressure; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; MRC: Medical Research Council; NIRS: near infrared spectroscopy; ROM: range of motion; SF36: Short Form-36; Ve: minute ventilation; Vt: tidal volume; Vt/T1: flow rates; Katz-ADL: The Katz index of independence in Activities of Daily Living. Scientific level of conclusion – Level 1: studies from A1 or minimal two A2 studies; Level 2: one A2 study or minimal two B studies; Level 3: one study from B or C; Level 4: opinion of expert.

DISCUSSION

We present the first evidence-based, expert driven and practical statement for the physiotherapy clinical reasoning process regarding motor functions and activities of intensive care patients. With that, this evidence statement provides evidence-based clinical recommendations regarding safety precautions, as well as the evaluation and treatment of musculoskeletal and cardiopulmonary functioning in intensive care, regardless of the medical diagnosis for which the patient was admitted to the intensive care unit. The levels of evidence are classified and provided.

This evidence statement follows the recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients.(37) In 2008, this task force identified targets for physiotherapy for intensive care patients and summarized the literature regarding the available effective physiotherapy interventions. With the discrepancies and lack of data on the efficacy of physiotherapy and of guidelines for physiotherapy assessments, there was a need to standardize pathways for clinical decision-making for physiotherapists.

Hanekom et al.(25) identified differences in clinical treatment strategies within and between countries.(25,56,57) They developed a clinical management algorithm for early physical activity and mobilization of intensive care patients in order to decrease clinical variability and to improve patient safety. These studies established important clinical tools for the early mobilization and activation in intensive care patients.(25,37) However, an evidence-based description of the clinical reasoning process and recommendations on the use of diagnostic tools and therapeutic interventions are still not available.

In addition to the available recommendations and algorithms, the present evidence statement provides explicit safety criteria for early mobilization, recommendations for the use of clinimetrics with psychometric properties and tailored interventions for relevant domains of functions and activities for intensive care patients based on the recent literature complemented with professional experience of intensive care physiotherapists and intensivists.

The strength of this evidence statement is that the recommendations are based on ‘strong’ (Level of 1 and 2) scientific evidence.(7,10,49,58) However, when ‘clinical experience’ was integrated in the recommendations, the strength, for example the safety criteria, reduced to ‘moderate strong’.

One could criticise our limited search strategy that only included literature from 1995. However, we assume that we did not miss relevant literature since the first study on the effects of activity in critically ill patients was published in 1995 by Griffiths.(38) After this publication, a growing number of studies have been published on early mobilization and activation of intensive care patients, which were included in our search.

Our aim was to provide a core set of clinimetrics within the ICF levels function and activities based on a 'strong' level of scientific evidence. With respect to the assessment of functions, instruments to measure cooperation, range of motion and muscle strength have been described to be appropriate for the use in intensive care patients, but instruments measuring sensation and muscle tone have not been investigated in an intensive care population.(34,35,37,59,60)

Several measures of activities have been proposed for the use in intensive care patients. The Physical Function ICU Test (PFITT), Barthel Index (BI) and the Functional Independence Measure (FIM) have been proven to be valid and reliable, but several items are not applicable for the use in patients with low level physical function, resulting in floor effects and low responsiveness if used in intensive care patients.(56,61–64) The Functional Status Score for the Intensive Care Unit (FSS-ICU) does contain relevant items for intensive care patients, such as bed mobility skills, but psychometric properties have not been established for an intensive care population.(63,65) A disadvantage of the above-mentioned instruments (PFITT, BI, FIM, and FSS-ICU) is that these instruments measure at an ordinal scale, which limits the quantification of changes in physical function.(63)

In the feedback rounds with the clinical experts, the DEMMI came forward to be used for measuring the ability to perform activities in intensive care patients.(66) The DEMMI measures mobility and its reliability, validity and absence of floor and ceiling effects have been shown in elderly hospitalized patients.(66) Although the psychometric properties of the DEMMI has not been established in intensive care patients, it was recommended because it is based on Rasch analysis, actually measuring real changes in functioning.(66) Moreover, validated translation versions of the DEMMI are available for different languages.(67) It is already part of standard physical therapy treatment in many hospitals in the Netherlands, which may facilitate the implementation for the use in intensive care patients.

In our opinion, the core set of instruments as proposed in this evidence statement is feasible and covers all relevant function and activity domains of critically ill patients.

In recent reviews and meta-analysis (11,68,69) the clinical relevant effects of physiotherapy interventions in intensive care patients for improving physical functioning have been described. In healthy adults, the detailed information regarding the FITT components has been described and transferred into guidelines, whereas owing to the complexity and changes of the acute conditions in intensive care patients, this remains lacking in this population.(70)

In the feedback rounds, physiotherapists and intensivists were asked to bring forward clinically relevant and feasible safety parameters to be used in the mobilization and activation of intensive care patients. These safety parameters might influence the training principles and involved FITT components. Safe and effective intensive care physiotherapy

treatment strategies, including FITT components, should be developed in the future, as well as knowledge regarding the pathophysiological mechanisms and the influence of training.

The present evidence statement on physiotherapy at the intensive care is limited to recommendations with respect to the treatment of primarily the musculoskeletal system, because in the current Dutch situation physiotherapists are primarily involved in the management of deconditioning. However, we realize that the physiotherapy domain may also involve the respiratory condition of intensive care patients.(37,71)

Patient preferences should also be considered in the development of clinical guidelines. For this evidence statement, the survey to identify relevant issues for evidence-based practice was only directed towards intensive care physiotherapists. Although respondents were united with respect to three priority clinical key questions, it would have been interesting to investigate whether these are also reflecting preferences among intensive care survivors.(72)

The strength of the recommendations within the evidence statement varies from moderate to strong. The methodological approach and the use of recent literature with a high level of evidence, supplemented with the feed-back from experienced physiotherapists and intensivists, ensures that the recommendations are evidence-based, as well as practical and feasible for the implementation in daily practice. Nevertheless, we believe that the evidence statement should be relevant for all intensive care patients.

Further research is recommended to determine the ideal dose and timing of exercise and the effect of exercise on specific conditions. Although the effectiveness of physiotherapy interventions is not for debate, the pathophysiological mechanisms of specific interventions and the dose – response relation in intensive care patients remains unknown.

Clinical messages

- Evidence and expert knowledge on patients in an intensive care unit has lead to:
- a set of criteria determining when it is safe to mobilize patients;
- a set of clinical parameters and nine specific standard assessments for use in this setting;
- recommendations on passive and active treatments to be used, and parameters to be monitored during treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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APPENDIX

1. Appendix Notes:

Note 1: Safety: "Red flags"

Strength of recommendation: moderate

The criteria for the recommendation (fig 2) have values 1 and 2.

The suggested criteria are of significance for the judgment of the hemodynamic stability, cardiorespiratory reserve and the level of awareness, to be able to safely mobilise out of bed and/or activate an intensive care patient.

Literature:

- Adler 2012: level: A1, Schweickert 2009: level A2, Burtin 2009: level B, Bourdin 2010: level C, Morris 2008: level C, Bailey 2007: level C, Brimioulle 1997: level C, Kasotakis 2012: level C, Hanekom 2011: level D, Nordon-Craft 2012: level D, Stiller 2003: level D, Kress 2009: level D, Leditschke 2012: level B, Needham 2010: level B, Balas 2014: level B, Damluji 2013: level C, Mah 2013: level B, Olkowski 2013: level C, Perme 2013: level B, Roth 2013: level B, Sricharoenchai 2014: level B, Wilcox 2013, level D, Rod 2013: level D.

Note 2: Clinimetrics for physical assessment

Responsiveness:

Strength of recommendation: Moderate

The recommendation to measure responsiveness values between 1 and 4.

Responsiveness shows the awareness and the ability of the patient to react to a task.

It is important to differentiate between cooperative and non-cooperative reactions.

To measure the responsiveness of the IC-patient, the following clinimetric tools are advised:

- Richmond Agitation Sedation Scale (RASS): Measures the awareness of the IC-patient: Scientific conclusion of value 1.
- Standardized Five Questions (S5Q): Measures the cooperation of the IC patient: Scientific conclusion of value 4.

Literature:

- Sessler 2002: level: reliability study, Ely 2003: level B, Adler 2012: level A1, Gosselink 2008, 2011: level D, Robinson 2013: level A1.

Joint mobility:
Strength of recommendation: Low
The recommendation to measure joint mobility has a value 4.
Evidence states that the risk of contractures increases, if range of motion (ROM) is not assessed in the first week of intensive care unit admission.

Active and passive ROM (AROM, PROM) should be measured with a goniometer according to the neutral-zero method and should measure large joints such as: Shoulder, elbow, wrist, hip, knee and ankle.

Literature:
- Ryf 1999: level D, Clavet 2008, 2011: level C, Gosselink 2008, 2011: level D.

Muscle strength:
Strength of recommendation: Moderate
The recommendation regarding the choice of measurement tools has value 2.
Measuring muscle strength in the intensive care is reliable (level 2).

The following clinimetric tools are advised to measure muscle strength in an intensive care patient

Musculoskeletal system:
- Manual Muscle Testing (MMT): MRC (sum)score
- Hand held dynamometer (HHD) or hand grip strength (Jamar) if an MRC-score of 3 has been reached

Literature:
- Nordon-Craft 2012: level D, Fan 2010: level: Hermans 2012: level: reliability study, Vanpee 2011: level: reliability study, Vanpee 2014: level A1, Baldwin 2013: level: reliability study.

Muscle tone:
Strength of recommendation: Low
The recommendation to measure muscle tone has value 4.
Literature has not reached consensus on what clinimetric tool to use to measure muscle tone in intensive care patients. The Dutch stroke guideline (KNGF richtlijn beroerte, 2014) recommends the Modified Ashworth Scale (MAS) to measure the resistance against passive movement.

The MAS can be used to assess the muscle tone of an intensive care patient in the intensive care setting.

- Modified Ashworth Scale (MAS)

Literature:

- Royal Dutch Physiotherapy Association (KNGF) guideline stroke 2014: level: guideline, Bohannon 1987: level: reliability study.

Sensibility:

Strength of recommendation: Low

The recommendation to measure sensibility has value 4.

Literature has not reached consensus regarding the measurement of sensibility, coordination and proprioception in intensive care patients. Burtin (2009) states that cycling 20 minutes daily on the ward might affect muscle coordination and thereby leading to improved physical functioning.

The Dutch stroke guideline (KNGF richtlijn beroerte, 2014) advises to use the (Modified) Nottingham Sensory Assessment (NSA) to test sensibility and proprioception.

The (Modified) Nottingham Sensory Assessment (NSA) can be used to assess the sensibility, coordination and proprioception in an intensive care patient in the intensive care setting.

- (Modified) Nottingham Sensory Assessment (NSA)

Literature:

- Royal Dutch Physiotherapy Association (KNGF) guideline stroke 2014: level: guideline, Bohannon 1987: level: reliability study.

Balance:

Balance will be evaluated within the de Morton Mobility Index (DEMMI). see: Note 2, functional status

Functional Status:

Strength of recommendation: Low

The recommendation has value 4.

No consensus has been met about the use of clinimetrics on the activity level in intensive care patients. Moreover, many measurement tools are not reliable and have not yet been validated for the intensive care population.

Many measurement tools have a floor or ceiling effect. This means that they are not applicable for the intensive care. In literature, many of these instruments are first being used after the patient has been discharged from the intensive care unit.

In elderly patients, the de Morton Mobility Index (DEMMI) has been used during hospital intake. This tool is able to detect small clinical differences, can be used from a low level, does not have a ceiling effect and does not need a lot of material or time for its performances.
The DEMMI includes items of the Berg Balance Scale (BBS), Barthel Index (BI) and the Functional Independence Measure (FIM).
To measure the level of activity in the intensive care, experts advice to use the DEMMI instead of the Functional Status Score for the Intensive Care Unit (FSS-ICU). The DEMMI has been tested on reliability and validity in the clinical setting (although only in elderly patients and not in the intensive care population).

The following clinimetric tools can be used to assess the level of activity of an intensive care patient in the intensive care setting:

- DEMMI

Literature:

- NICE: level guideline, Adler 2012: level A1, Nordon-Craft 2012: level D, Thomas 2009 and 2011: level A2, Burtin 2009: level B, Kasotakis 2012: level C, Winkelman 2012: level B, Zanni 2010: level C, Gosselink 2008: level D, Gosselink 2011: level D, De Morton 2008: level reliability study, Denehy 2013: level reliability study, Tipping 2012: level D, Hodgson 2014: level D, Trush 2012: level B.

Note 3: Interventions

Strength of recommendation: Low
The recommendations given for physiotherapeutic treatments are based on literature with values 1, 2, 3 and expert opinions.

The effects of physiotherapeutic interventions on deconditioning of intensive care patients are based on values of 1, 2 and 3 (see table 2).
Effects on the level of anatomical features, such as preventing a decrease in protein levels and an increase in inflammatory inhibitors, can be reached through minimally training the muscles actively or passively or by using a Continuous Passive Motion (CPM) for 20 minutes.

Literature:

- Hanekom 2011: D, Schweickert 2009: level A2, Gruther 2010: level A2, Gerovasili 2009: level B, Karatzanos 2012: level B, Poulsen 2011: level B, Routsi 2010: level B, Martin 2011: level A2, Cader 2010: level B, Caruso 2005: level B, Burtin 2009: level B, Morris 2008: level C, Chang 2005: level C, Moodie 2011: level A1, Griffiths 1995: level B, Meesen 2010: level B, Winkelman 2012: level B, Reid 2004: level B, Clavet 2008 and 2011: level C, Gosselink 2008, 2011: level D, Moree 2011: level D, Heather 2008: level D, Genc 2012: level B, Chang 2011: level B, Zafiropoulos 2004: level C, Stiller 2004: level C, Kraemer 2002: level D, Kho 2012: level D, Romer 2003: level B, Amidei 2013: level B, Angelopoulos 2013: level B, Calvo-Ayala 2013: Level A2, Camargo Pires-Neto 2013: level D, Chen 2012: level B, Hermans 2014: level A1, Parry 2013: level A1, Kayambu 2013: level A1, Li 2013: level A1, Hirose 2013: level B, Stockley 2012: level D, Stiller 2013: level D, Rodrigues 2012: level B, Williams 2014: level A1.

Note 4: Recommendation of qualitative and quantitative training aspects

No evidence available in detail in intensive care patients.

Due to the fact that there are insufficient foundations on parameters of training and exercise physiology in the intensive care, no recommendations can be provided on training variables and progression in in training to increase the musculoskeletal and cardiopulmonary systems in intensive care patient.

In order to guarantee the safety during training, it is advised to monitor the criteria on when to terminate training (see note 6).

It is advised to monitor and evaluate the effort with the use of the duration, number of repetitions and the BORG scale (see note 7) (scientific conclusion of level 3 and 4)

Literature:

- Morree 2011: level D, Burtin 2009: level B, Winkelman 2012: level B, Morris 2008: level C, Hanekom 2011: level D, Babb 2012: level D, Kraemer 2002: level D, Gosselink 2008: level D, Amidei 2012, level D.

Note 5: Parameters

Strength of recommendation: Moderate

The parameters have values 1 and 2

The following recommendation parameters are necessary to monitor the safety of an intensive care patient during mobilization and activity.

Clinical view:

- Decreased level of awareness/consciousness
    - Sweating
    - Abnormal face colour
    - Pain
    - Fatigue
- Heart rate
- Blood pressure
- Oxygen saturation
- Respiratory frequency

Literature:

- Hanekom 2011: level D, Adler 2012: level A1, Schweickert 2009: level A2, Stiller 2003 and 2007: level D, Brimioulle 1997: level B, Kasotakis 2012: level C, Winkelman 2012: level B, Bourdin 2010: level C, Bailey 2007: level C, Thomsen 2008: level C, Kress 2009: level D, Burtin 2009: level B, Zanni 2010: level C.

Note 6: Termination criteria

Strength of recommendation: Moderate
The recommendation has values 1 and 2

The criteria to terminate exercise with an intensive care patient are of importance to assess the load of the cardiorespiratory system of an intensive care patient.

It is advised to terminate treatment if the following criteria are met:

- Heart rate: <40; > 130
- Blood pressure (MAP): < 65 mmHg; > 110 mmHg
- Respiratory frequency: > 40 p/min
- Oxygen Saturation: < 90%
- Arrhythmia
- Clinical symptoms:
    - Decreased level of awareness/consciousness
    - Sweating
    - Abnormal face colour
    - Pain
    - Fatigue

Literature:

- Adler 2012: level A1, Schweickert 2009: level A2, Winkelman 2012: level B, Burtin 2009: level B, Bourdin 2010: level C, Morris 2008: level C, Stiller 2003 level: D, Hanekom 2011: level D, Mah 2013: level B.

Note 7: Evaluation of interventions

Strength of recommendation: Moderate

The recommendation related to the monitoring of safety have value 1 and 2. In relation to physiotherapeutic interventions, with value 3 and 4.

The recommended parameters are of importance for safe treatment, monitoring and evaluating the physiotherapeutic interventions of an intensive care patient.

The following parameters may be used to monitor, assess and/or evaluate the intensity of the effort on the intensive care patient:

- Clinical view:
    - Decreased level of awareness/consciousness
    - Sweating
    - Abnormal face color
    - Pain
    - Fatigue
- Heart rate
- Blood pressure
- Oxygen saturation
- Respiratory frequency
- Tidal volume
- Treatment frequency
- Number of repetitions
- Number of sets
- Duration of the activity
- BORG scale

Literature:

- Hanekom 2011: level D, Adler 2012: level A1, Schweickert 2009: level A2, Stiller 2003 and 2007: level D, Brimioulle 1997: level B, Kasotakis 2012: level C, Winkelman 2012: level B, Bourdin 2010: level C, Bailey 2007: level C, Thomsen 2008: level C, Kress 2009: level D, Burtin 2009: level B, Zanni 2010: level C, Morree 2011: level D, Gosselink 2008: level D, Amidei 2012, level D

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3. Appendix: work cards diagnostic and therapeutic process

Work card: Physiotherapy clinical reasoning regarding the diagnostic process

Diagnostic Process	It is recommended to screen every patient on the presence of red flags (contraindications) and relative contra-indications to consider (possible) risks and benefits before and during every physiotherapy treatment session.
Screening	The criteria mentioned below are (relative) contra indications for mobilizations out of bed and physical activities of intensive care patients and have to be taken into consideration during the clinical reasoning process.
(Additional) patient history	An intensivist needs to be consulted in case of a patient showing one of the following conditions before mobilization/physical activities.

Red Flags (level 1)

Heart rate

- Recent myocardial ischemia
- Heart rate < 40 and > 130

Blood pressure

- MAP < 60 mmHg and > 110 mmHg

Oxygen saturation

- ≤ 90%

Parameters of ventilation

- $FiO_2 \geq 0.6$
- PEEP: ≥ 10cm H_2O

Respiratory frequency

- Respiratory frequency > 40 p/min

Level of consciousness of patient

- RASS score: -4, -5, 3, 4

Doses inotropic

- High inotrope doses
  - Dopamine ≥ 10 mcg/kg/min
  - Nor/adrenaline ≥ 0,1mcg/kg/min

Temperature

- ≥ 38.5°C
- ≤ 36°C

Relative contra-indications (level 3 and 4)

- Clinical View
  - Decreased level of awareness/consciousness
  - Sweating
  - Abnormal face color
  - Pain
  - Fatigue
- Unstable fractures
- Presence of lines that make mobilization unsafe.
- Neurological instability: ICP ≥ 20 cmH_2O

Physiotherapeutic assessment of functional movement	It is recommended to use these clinimetrics when needed for evaluate impairments and activities restrictions within the ICF classification.
	
	Assessment of the musculoskeletal system
	○ Edema, muscle atrophy, contractures, deformities, bed sores, decubitus, wounds
	
	Assessment
	Function
	○ Cooperation
	  ○ S5Q (level 4)
	○ Active and Passive limitations in ROM
	  ○ ROM (level 4)
	○ Muscle strength
	  ○ MRC (sum) score (level 2)
	  ○ Hand held dynamometer or hand grip strength (Jamar) if MRC score of 3 has been reached (level 2)
	○ Muscle tone
	  ○ MAS (level 4)
	○ Sensibility
	  ○ NSA (level 4)
	
	Activities
	• Transfers
	  ○ DEMMI (level 4)
	• Walking
	  ○ DEMMI (level 4)

Work card: Physiotherapy clinical reasoning regarding the therapeutic process

Therapeutic process	**Non-responsive and non-cooperative patient** • Rass Score < -2 (level 2) • S5Q < 3 (level 4)	**Responsive and adequate patient** • Rass Score ≥ -2 (level 2) • S5Q ≥ 3 (level 4)
Treatment plan	**Passive (Note 3)** • Passive Exercise (level 2) o Repetitions: 5 times/joint o Sets: 1 o Frequency: Once daily • Stretching (level 2) o Duration: 20 minutes • Passive cycling (level 2) o Duration: 20 minutes • EMS (level 1 and 2) o Duration: 60 minutes o Intensity: 45 Hz o Frequency: Daily • CPM (level 2) o 3 x 3 hours daily • Splinting (level 4) o Duration: 2 hours on and 2 hours off	**Active (Note 3)** • Exercise Therapy (level 4) • Intensity: (level 4) BORG 11 - 13 • Duration: (level 4) Repetitions: 8 – 10 repetitions • Sets: 3 (level 4) BORG 11 - 13 • Frequency: 1 – 2 times daily (level 4) BORG 11 - 13 • Build up (level 4) Step 1: Increase duration o Increase repetitions to 10 Step 2: Increase number of sets o From 1 set to 3 sets Step 3: Increase intensity o From BORG score 11 to 13 Step 4: Increase frequency o From once daily to twice daily • ADL training: Balance, standing, walking (level 3) • Out of bed mobilization (level 2) • Cycling (level 2) o Duration: 20 minutes o Build up: Build up interval training towards 20 minutes

Treatment process	**During the interventions, parameters of safety and effort should be monitored and evaluated (Note 4, 5, 6, 7)**	
	o Heart rate (level 1) o Blood pressure (level 1) o Respiratory frequency (level 1) o Oxygen saturation (level 1) o Change in clinical symptoms such as: (level 3 and 4) Level of awareness/consciousness Sweating Abnormal face color Pain Fatigue	Screening continues
	o Duration of the intervention (level 4) o Number of repetitions (level 4) o Number of sets (level 4) o Frequency of the intervention(s) (level 4) o BORG-score (level 4)	After the treatment
	It is advised to stop therapy if the following criteria are met: (level 1) o Heart rate: < 40; > 130 o Blood pressure MAP: 65 mmHg; > 110mmHg o Respiratory frequency: > 40/min o Oxygen saturation: < 90% o Arrhythmia Each therapy session should be evaluated on the basis of the diagnostic and therapeutic process.	

CHAPTER 3

De Morton Mobility Index is feasible, reliable, and valid in patients with critical illness

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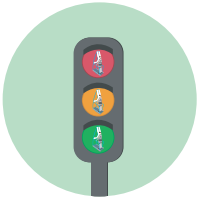

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ABSTRACT

Background. Intensive care unit (ICU) stays often lead to reduced physical functioning. Change in physical functioning in patients in the ICU is inadequately assessed through available instruments. The de Morton Mobility Index (DEMMI), developed to assess mobility in elderly hospitalized patients, is promising for use in patients who are critically ill.

Objective. The aim of this study was to evaluate the clinimetric properties of the DEMMI for patients in the ICU.

Design. A prospective, observational reliability and validity study was conducted.

Methods. To evaluate interrater and intrarater reliability (intraclass correlation coefficients), patients admitted to the ICU were assessed with the DEMMI during and after ICU stay.
Validity was evaluated by correlating the DEMMI with the Barthel Index (BI), the Katz Index of Independence in Activities of Daily Living (Katz ADL), and manual muscle testing (MMT).
Feasibility was evaluated based on the percentage of participants in which the DEMMI could be assessed, the floor and ceiling effects, and the number of adverse events.

Results. One hundred fifteen participants were included (Acute Physiology and Chronic Health Evaluation II [APACHE II] mean score=15.2 and Sepsis-related Organ Failure Assessment [SOFA] mean score=7). Interrater reliability was .93 in the ICU and .97 on the wards, whereas intrarater reliability during the ICU stay was .68. Validity (Spearman rho coefficient) during the ICU stay was .56, -.45, and .57 for the BI, Katz ADL, and MMT, respectively. The DEMMI showed low floor and ceiling effects (2.6%) during and after ICU discharge. There were no major adverse events.

Limitations. Rapid changes in participants' health status may have led to underestimation of intrarater reliability.

Conclusion. The DEMMI was found to be clinically feasible, reliable, and valid for measuring mobility in an ICU population. Therefore, the DEMMI should be considered a preferred instrument for measuring mobility in patients during and after their ICU stay**.**

Due to critical illness and prolonged inactivity, survivors of the intensive care unit (ICU) often show decreased physical functioning and mobility, limiting their daily activities and quality of life.(1–3) Previous research has shown the effectiveness of physical therapy interventions in patients who are critically ill. Early stimulation of physical activity and mobilization decreased the duration of mechanical ventilation, delirium, and length of stay in the ICU and hospital and improved physical functioning and quality of life.(4–7)

To facilitate physical therapy goal setting and the evaluation of the recovery process in patients in the ICU, an accurate assessment of physical activities of patients in the ICU based on the domains of the *International Classification of Functioning, Disability and Health* (ICF) framework is required.(8,9) The ICF framework consists of 3 core domains to describe the level of functioning: (1) body functions and structures, (2) activities, and (3) participation.(8,9) It also has been proposed as a model in which measurements can be organized.(8,9) Measuring physical activities in patients in the ICU is complex due to the different stages of the disease, which influences task completion, coordination, processing of visual information, and central and peripheral motor drive.(8) The instruments frequently used for physical measuring activities within the ICF domain in the ICU are the Barthel Index (BI), the Katz Index of Independence in Activities of Daily Living (Katz ADL), the Physical Function ICU Test (PFIT), and the Functional Status Score for the Intensive Care Unit (FSS-ICU).

The BI and the Katz ADL are frequently used to measure activities in clinical settings and are reliable and valid tools, measuring physical performance capacity of 10 basic activities of daily living (ADL).(10,11) These are multidimensional instruments for measuring ADL tasks (eg, transfers, mobility, stair climbing), but some activities are not applicable for all patients in the ICU (eg, bladder and bowel function, bathing, clothing, stair climbing). The PFIT is also a reliable and valid instrument (intraclass correlation coefficient [ICC]= 1, minimal clinically important difference = 1.5/10 points) for measuring physical activities (eg, muscle strength, coming to a standing position, walking) in patients in the ICU.(12) Patients entering the ICU who are not capable of performing transfers or coming to a standing position may not be able to perform the activities tested by the PFIT. The PFIT contains items that are too difficult for many patients who are critically ill, such as performing out of-bed tasks, resulting in notable floor effects within the ICU and ceiling effects from 20% at discharge.(12) The FSS-ICU is primarily designed to measure the physical performance of low-level activities (eg, rolling, supine-to-sit transfers, unsupported sitting, sit-to-stand transfers, ambulation).(13) Clinimetric properties of this instrument have not yet been reported. In summary, the currently available instruments are not fully appropriate for measuring the level of activities of patients who are critically ill during the various stages

of recovery because they include items that may be too difficult (eg, walking, dressing) or lack relevant ICU activities such as bed mobility skills (eg, rolling, transfer from supine to sitting position, sitting balance).(8) These limitations result in “floor effects” (the inability of a test to measure below a certain point because its items are too difficult) in scores observed in the ICU and “ceiling effects” (the inability of a test to measure above a certain point because its items are too easy) after
discharge.(8,14)

The de Morton Mobility Index (DEMMI) was originally developed to measure the full range of mobility within the ICF activity domain in elderly patients admitted to the hospital.(15) It consists of 15 hierarchical mobility items (3 bed, 3 chair, 4 static balance, 2 walking, and 3 dynamic balance items). The total score is converted with Rasch analysis to an interval score ranging from 0 to 100, where 0 represents poor mobility and 100 indicates high levels of independent mobility. The DEMMI is a freely available at http://www.demmi.org.au. However, it includes items that also appear to be relevant and feasible for patients who are critically ill in the ICU (eg, bed mobility and transfers) and after ICU discharge (eg, ambulation and jumping). It seems feasible, therefore, to evaluate recovery throughout the rehabilitation trajectory during and after an ICU stay.(8) The unidimensionality of the DEMMI was confirmed by Rasch modelling, and the instrument showed strong clinimetric properties within a diverse range of elderly people with acute and chronic illnesses in different settings (clinical ward, rehabilitation, and community).(15–20) A Dutch translation of the DEMMI was validated and found to be reliable.(18)

Due to the lack of a suitable instrument for measuring activities in patients in the ICU in detail, and in view of the promising measurement properties of the DEMMI in various hospital populations and rehabilitation and community settings, the aim of this study was to evaluate the feasibility, reliability, and validity, focusing especially on floor and ceiling effects of the DEMMI in a population in the ICU.

METHOD

Study Design and Setting

This prospective, observational reliability and validity study was performed in the Academic Medical Center (AMC) in Amsterdam, a 1,000 bed university hospital with 34-bed mixed medical and surgical format ICUs and medium intensive care units (M-ICUs). Patients in the M-ICU of the AMC characteristically are off mechanical ventilation but still require a high level of care and full-time monitoring. Measurements were performed within the ICU and M-ICU and on the regular wards until hospital discharge.

Participants

In a 3-month period (November 2013– January 2014), we included all consecutive adult patients (age 18 years or older) admitted to the ICU and M-ICU who were referred for physical therapy. Patients admitted for 24 hours at the ICU or M-ICU and for whom it was safe to perform physical exercises according to the safety criteria as described in the evidence statement by Sommers et al (21) (Appendix) were included in the study.

Exclusion criteria were neurological or neurosurgical admission diagnosis, imminent death, and insufficient comprehension of the Dutch language. Sample size calculations indicated that 101 participants were needed to estimate the ICC statistics with 95% confidence (+/-0.2%) around the point estimate, assumed to be .70.(22)

Procedure

Participant characteristics (sex, age, medical category, and Sepsis-related Organ Failure Assessment [SOFA] score) were recorded from the medical charts. Participants were measured at 2 time points: at admission to the ICU or M-ICU ($T0_{ICU}$ and $T0_{M\text{-}ICU}$) and after discharge from the ICU or M-ICU at the regular hospital ward (T1). The interrater reliability of the DEMMI was evaluated by simultaneous and independent measurements by 2 physical therapists at T0 and T1. The DEMMI was executed according to the standard procedure as described by de Morton at al.(15) One physical therapist provided the instructions and guided the patient, while the other therapist observed without interference. Therapists were blinded from each other's scoring forms. To examine intrarater reliability, each measurement was repeated by both assessors within a 1-hour assessment at T0 to reduce the influence of fatigue and the occurrence of rapid changes in medical conditions. Data from all of the assessments were entered into a database by a researcher who was not involved in the assessments. To evaluate validity, the BI, Katz ADL, and manual muscle testing (MMT) using the Medical Research Council sumscore (MRC-SS) were administered by a physical therapist at all assessment occasions. The MRC-SS has a total score ranging from 0 to 60 points obtained from bilateral testing of 6 muscle groups, where the minimal score is 0 (indicating no muscular contraction) and the maximum score is 5 (indicating normal muscle strength). In the sequence of performing measures, we started with MMT, followed by questioning items of the Katz ADL and the BI and, after a rest period of 30 minutes, measuring the items of the DEMMI. All assessments were performed by 6 trained and experienced ICU physical therapists involved in the treatment of patients in the ICU. The feasibility of the DEMMI was measured by recording the number of patients who were referred for physical therapy for whom the DEMMI could be administered and the adverse events that occurred during the measurements (eg, fall to knees or ground, loss of consciousness, cardiac arrest, dislodgement of medical equipment) and by analysis of floor and ceiling effects at the ICU and the regular hospital ward.

Assessments

The raw DEMMI (a 15-item unidimensional measure of mobility, ranging from 0 to 19 points) was Rasch converted to a 0 to 100 interval scale. A score of 0 indicates no mobility, and a score of 100 points represents full mobility.(15) The Dutch-translated version of the original DEMMI was used, which has shown validity and reliability coefficients similar to those of the original version.(15,18) The BI and the Katz ADL were used to assess ADL.(23) The BI consists of 10 items, ranging from 0 to 20 points, with a higher score indicating better functioning.(24) This index includes 2 mobility-related items that are also part of the DEMMI, as well as additional items on ADL and bladder- and bowel incontinence. The Katz ADL consists of 6 items on ADL and incontinence. A score of 0 indicates that the patient is independent in performing ADL, and a score of 6 points indicates full dependence for these activities.(25,26)

Manual muscle testing was used to assess muscle weakness and was performed according to the scoring system of the Medical Research Council scale for muscle strength (MRC), in which a score of 0 indicates no contraction and the maximum score of 5 indicates contraction against strong resistance.(27,28) For measuring the MRC-SS, 6 muscle groups were assessed bilaterally: abduction of the arm, flexion of the elbow, dorsiflexion of the wrist, flexion of the hip, extension of the knee, and dorsiflexion of the ankle. The total score ranges from 0 to 60 points; a cutoff point of < 48 points was used to indicate significant muscular weakness, and a score of < 36 points indicates severe muscular weakness.(28) The BI, Katz ADL, and MMT served as convergent validity measures of the DEMMI. To classify the severity of the disease at ICU admission, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used. The APACHE II is a severity-of-disease classification system based on physiological measurements, such as body temperature, respiratory rate, and white blood cell count.(29) The total score ranges from 0 to 71 points, where higher scores correspond to more severe disease.(29) The APACHE II does not include items on mobility; therefore, it was used to assess the divergent validity of the DEMMI.

Data Analysis

The interrater and intrarater reliability of the DEMMI total score were calculated using the one-way random ICC model. Kappa values were calculated to evaluate the reproducibility of items with a binary response scale, and weighted kappa values with quadratic weights were calculated for items 3, 5, 11, and 12, having a polytomous response scale.

Convergent validity was calculated by using Spearman rho correlation coefficients for the DEMMI with the BI, Katz ADL, and MMT. Divergent validity was evaluated likewise for the DEMMI with the APACHE II score. A high correlation was defined as having a rho correlation

coefficient of 1, a strong correlation was defined as having a rho correlation coefficient of .7 to .9, and a moderate correlation was defined as having a rho correlation coefficient between .4 and .6.(30) Known-groups validity (that is, validity for groups that would be expected to differ in their mobility) of the DEMMI was assessed using the following ICU acquired weakness (ICU-AW) categories: MRC-SS cutoff point < 36 (severe weakness), MRC-SS cutoff point < 48 (significant weakness), and MRC-SS values ≥ 48 (no weakness). (28,31) The Kruskal- Wallis test and eta-squared effect sizes (ES; 0.02=small, 0.13=medium, and > 0.26=large) were used to assess the ability of the DEMMI, BI, and Katz ADL to detect differences in ICU-AW score groups.(32) Post hoc Mann-Whitney *U* tests with Bonferroni corrections were performed to analyze possible statistical differences between the ICU-AW subgroups detected by the DEMMI.

Feasibility of the instruments in the ICU sample (ie, their content validity or the extent to which the measures are targeted to the sample) was evaluated by examining score distributions and by plotting histograms with normal curves and calculating the percentage of participants with a minimum or maximum score.

Sensitivity to change was analyzed by calculating the minimal detectable change at the 90% level of confidence (MDC_{90}). The MDC_{90} should suffice in patients who are critically ill, where safety criteria were already applied, and to track improvement in rehabilitation. By calculating the MDC_{90}, comparison with earlier reported sensitivity to change is possible (eg, MDC_{90}=8.9 in study by de Morton et al (15)).(33)

All statistics were interpreted as significant with *P* values of .05 or lower and associated 95% confidence intervals (95% CIs). Statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, New York).

RESULTS

During the 3-month inclusion period, 361 patients were admitted to the ICU or M-ICU; 246 of these patients were excluded because they did not meet the inclusion criteria (Fig. 1).

In total, 115 eligible patients participated in this study, of whom 77 (67%) were admitted to the ICU and 38 (33%) to the M-ICU (Tab. 1). Fifty-three percent of the included patients were admitted due to elective surgery (scheduled thoracic and abdominal surgery), 33% due to medical indications (sepsis, respiratory insufficiency due to pneumonia, and infectious diseases), and 14% due to nonelective surgery. The baseline scores and interquartile ranges of the DEMMI, BI, and Katz ADL are presented in Table 1. Of the 115

patients at T0, 86 were assessed after a mean of 6 days (SD=9) at the regular hospital wards at T1. A flowchart of the study sample is provided in Figure 1. During the measurements at T0 and T1, no major adverse events were reported. The administration of the DEMMI could be performed in all patients in the ICU and in patients at the regular hospital ward.

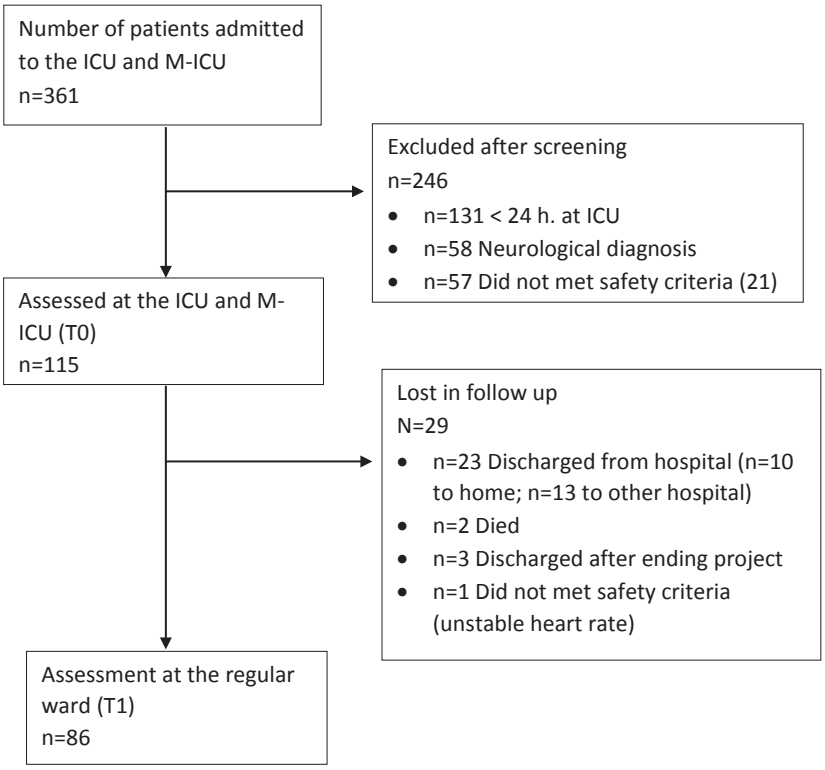


Figure 1 Flowchart of study population and measurements
T0=time of inclusion in either the intensive care unit (ICU) or the medium ICU (M-ICU), T1= time after discharge from the ICU or M-ICU at the regular hospital ward.

Table 1 Characteristics of the study population at admission to the (M-)ICU (T0) and regular hospital wards (T1)[a]

Characteristic	$T0_{ICU}$ n = 77 (67%)	$T0_{M\text{-}ICU}$ n = 38 (33%)	$T0_{Total}$ n = 115 (100%)	T1 n =86 (75%)
Male, n (%)	55 (71)	22 (58)	77 (67)	53 (61.6)
Age (y), $\bar{X}$ x(SD)	63 (15.8)	58 (16.6)	61 (16.1)	62 (14.7)
Medical category, n (%)				
Medical	33 (42.9)	5 (13.2)	38 (33)	24 (27.9)
Nonelective surgery	11 (14.3)	5 (13.2)	16 (14)	14 (16.3)
Elective surgery	33 (42.9)	28 (73.7)	61 (53)	48 (55.8)
APACHE II $\bar{X}$x (SD)	16.2 (4.6)	12.6 (4.4)	15.2 (4.8)	NA
SOFA, $\bar{X}$ x(SD)	7 (3.7)	4 (2.3)	7 (3.6)	NA
DEMMI, median (IQR)	27 (22-32)	30 (24-36)	30 (24-33)	48 (33-62)
Barthel Index, median (IQR)	3 (1-6)	5 (3-7)	4 (1-6)	11 (7-15)
Katz-ADL, median (IQR)	5 (4-6)	4 (4-5)	4 (4-6)	2 (0-4)
MRC-SS, median (IQR)	52 (46.5-55.5)	54 (49.5-56)	52 (47-5)	55 (51-58)
No weakness, MRC-SS 48-60, n (%)	52 (67.5)	30 (78.9)	82 (71.3)[b]	74 (86)
Significant weakness, MRC-SS 36-47 n (%)	13 (16.9)	8 (21.1)	21 (18.3)[b]	10 (11.6)
Severe weakness, MRC-SS < 36, n (%)	8 (10.4)	0 (0)	8 (7)[b]	1 (1.2)

[a] ICU=intensive care unit, M-ICU = medium intensive care unit, $T0_{ICU}$=time of inclusion in the intensive care unit, $T0_{M\text{-}}$ICu= time of inclusion in the M-ICU, T1= time after discharge from the intensive care unit or M-ICU at the regular hospital ward, N/A= not available, IQR= interquartile range, APACHE II=Acute Physiology and Chronic Health Evaluation II, SOFA=Sepsis-related Organ Failure Assessment,
DEMMI=de Morton Mobility Index, Katz ADL=Katz Index of Independence in Activities of Daily Living, MRS-SS=Medical Research Council sum-score, MRC=Medical Research Council scale for muscle strength as tested by manual muscle testing.
[b] MRC-SS scores missing for 4 participants (3.4%).

The interrater and intrarater reliability of the DEMMI sum-scores and item scores during the assessments are presented in Table 2. The interrater reliability was .93 at T0 and .97 at T1. The intrarater reliability was .68 at T0. Reproducibility of the DEMMI items ranged from .52 for item 4 (sit unsupported in chair) to 1.00 for items 9, 10, 13, and 15 (Tab. 2). Similar kappa values were found at T1.

Convergent, divergent, and knowngroups validity coefficients are presented in Table 3. For the BI, Katz ADL, and MMT with the DEMMI, the convergent validity coefficient was 0.56, -0.45, and 0.57, respectively, at T0 and 0.75, -0.76, and 0.63, respectively, at T1. Divergent correlation with the APACHE II score was -0.18.

Table 2 Clinimetric properties of the DEMMI and reproducibility of the DEMMI at each assessment[a]

Measure	T0 n= 115	T1 n= 86
Reliability		
Interrater (ICC [1,1])	.93 (.91-.95)	.97 (.96-.98)
Intra-rater (ICC [1,1])	.68 (.46-.82)	[b]
Agreement (*k* or *k*W) [c]		
Item 1 (bridge)	.79	.95
Item 2 (roll onto side)	.87	.78
Item 3 (lying to sitting)	.80	.92
Item 4 (sit unsupported in chair)	.52	[d]
Item 5 (sit to stand from chair)	.77	.94
Item 6 (sit to stand without using arms)	.82	.91
Item 7 (stand unsupported)	.91	1.00
Item 8 (stand with feet together)	.86	1.00
Item 9 (stand on toes)	1.00	1.00
Item 10 (tandem stand with eyes closed)	1.00	.90
Item 11 (walking distancewith/without gait aid)	.96	.97
Item 12 (walking independence)	.66	.95
Item 13 (pick up pen from floor)	1.00	.95
Item 14 (walks 4 steps backwards)	.78	.94
Item 15 (jump)	1.00	.90

[a] ICC [1,1]=one-way random intraclass correlation coefficient, DEMMI=de Morton Mobility Index, T0=time of inclusion in either the intensive care unit (ICU) or the medium ICU (M-ICU), T1=time after discharge from the ICU or M-ICU at the regular hospital ward.
[b] Was not determined.
[c] Kappa (*k*) values were reported for all items, except for polytomous items 3, 5, 11, and 12, for which weighted kappa (*k*W) values were reported.
[d] Could not be calculated due to low variances in scores.

For known-groups validity, significant differences (Kruskal-Wallis test, $P<.001$) in DEMMI scores were observed among the ICU-AW categories (Tab. 3). The etasquared ES for the relationship with ICU-AW groups was 0.22 for the DEMMI, 0.14 for the BI, and 0.17 for the Katz ADL at T0. These eta-squared ES values were similar to those found at T1, as shown in Table 3. Post hoc analysis showed that the DEMMI was able to differentiate among the 3 ICU-AW categories at T0 and T1 (Tab. 3). However, the DEMMI showed no significant ability to differentiate between severe and significant weakness ($P=1.00$) at T1. Also, no significant differences were observed between the severe weakness group and the no weakness group at T1.

Table 3 Clinimetric properties of the DEMMI and validity of the DEMMI at each assessment[a]

Measure	T0 n= 115	T1 n= 86
Convergent validity (rho, 95% CI)		
Barthel index	0.56 (0.42-0.67)	0.75 (0.63-0.83)
Katz-ADL	-0.45 (-0.59 - -0.29)	-0.76 (-0.84- -0.65)
MMT (MRC-SS)	0.57 (0.43-0.69)	0.63 (0.48-0.75)
Divergent validity (rho, 95% CI)		
APACHEII (n=97)	-0.18 (-0.36-0.01)	NA
Known groups differences[b] by MRC-SS groups[c]		
DEMMI, ES (*P*-value)	0.21 ($p \leq .001$)	0.20 ($p \leq .001$)
Barthel Index, ES (*P*-value)	0.14 ($p \leq .001$)	0.15 ($p = .002$)
Katz-ADL, ES (*P*-value)	0.17 ($p \leq .001$)	0.16 (p=.001)
Post-hoc known-groups differences for the DEMMI[d]		
Severe weakness vs. significant weakness[b]	$p = .03$	$p = 1.00$
Severe weakness vs. no weakness[b]	$p \leq .001$	$p = .21$
Significant weakness vs. no weakness[b]	$p = .07$	$p \leq .001$

[a] DEMMI=de Morton Mobility Index, T0=time of inclusion in either the intensive care unit (ICU) or the medium ICU (M-ICU), T1=time after discharge from the ICU or M-ICU at the regular hospital ward, CI=confidence interval, Katz ADL=Katz Index of Independence in Activities of Daily Living, MMT=manual muscle testing, MRS SS=Medical Research Council sum-score, APACHE II=Acute Physiology and Chronic Health Evaluation II, ES=effect size, N/A= not available.

[b] Known-groups validity shown by eta-squared ES values, and *P* values were used to detect difference in ICU-acquired weakness (ICU-AW) score groups with the various measurements.

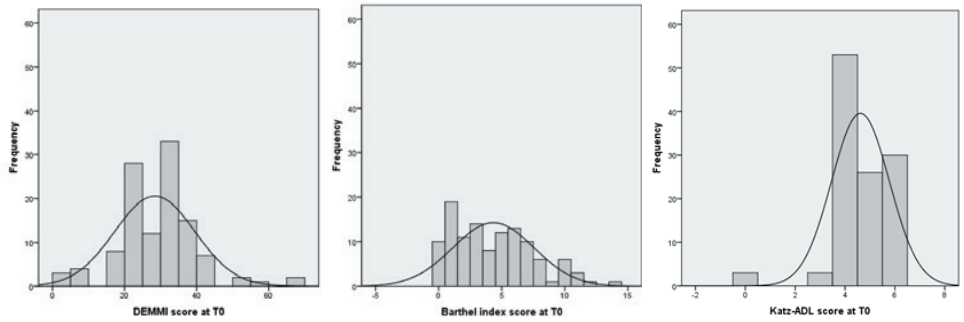
[c] Known-groups validity based on the MRC-SS groups: no weakness (48–60 points), significant weakness (36–47 points), severe weakness (<36 points).

[d] Post hoc analysis based on Mann-Whitney U scores with Bonferroni corrections; *P* values were reported.

The score distributions of the DEMMI, Katz ADL, and BI for the different assessment occasions are presented in Fig. 2. At T0, a floor effect was shown in 30 participants (26.1%) in the Katz-ADL results and in 10 participants (8.7%) for the BI, whereas the DEMMI showed the lowest proportion of the floor effect in 3 participants (2.6%). Ceiling effects were observed only in the Katz ADL scores in 3 participants (2.6%) at T0 (Fig. 2A). At T1, the DEMMI scores did not show a floor effect, whereas the BI scores showed one participant (0.9%) with the lowest score. The Katz ADL had a floor effect in 4 participants (3.5%). At T1, the Katz ADL scores showed 22 participants (19.1%) with a ceiling effect, whereas a low ceiling effect was shown by the DEMMI in 3 participants (2.6%), and the BI did not show any ceiling effects (Fig. 2B).

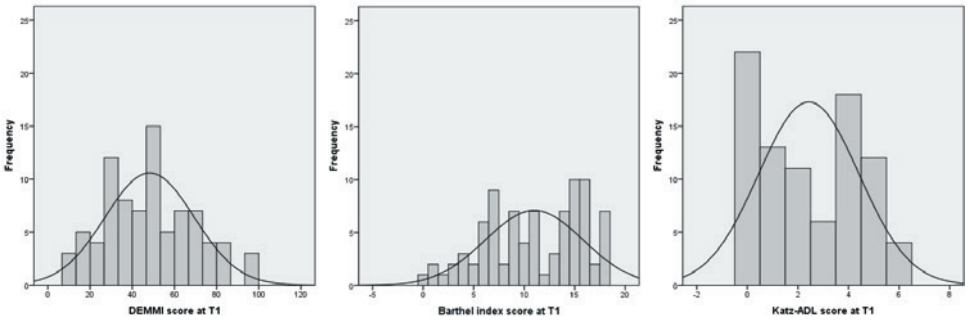
The MDC_{90} score for sensitivity to change was 6.73 points at T0 (Tab. 4). This value was similar to that at T1 at the regular hospital ward, where 8.23 points was found for the MDC_{90} score.

A



DEMMI: floor effects: n=3 (2.6%); ceiling effects: n=0 (0%)
Barthel index: floor effects: n=10 (8.7%); ceiling effects: n=0 (0%)
Katz-ADL: floor effects: n=30 (26.1%); ceiling effects: n=3 (2.6%)

B



DEMMI: floor effects: n=0 (0%); ceiling effects: n=3 (2.6%)
Barthel index: floor effects: n=1 (0.9%); ceiling effects: n=0 (0%)
Katz-ADL: floor effects: n=4 (3.5%); ceiling effects: n=22 (19.1%)

Figure 2 Floor and ceiling effects of the de Morton Mobility Index (DEMMI), Barthel Index, and Katz Index of Independence in Activities of Daily Living (Katz ADL)
(A) at time of inclusion in either the intensive care unit (ICU) or the medium ICU (M-ICU) (T0) and (B) at time after discharge from the ICU or M-ICU at the regular hospital ward (T1).

Table 4 Clinimetric properties of the DEMMI and sensitivity to change of the DEMMI at each assessment[a]

Measure	T0 n = 115	T1 n = 86
SD	10.85	20.76
SEM	2.89	3.54
MDC_{90}	6.73	8.23

[a] DEMMI=de Morton Mobility Index, T0=time of inclusion in either the intensive care unit (ICU) or the medium ICU (M-ICU), T1=time after discharge from the ICU or M-ICU at the regular hospital ward, SD=pooled standard deviation between raters, SEM=standard error of the measurement, MDC_{90}=minimal detectable change at 90% level of confidence.

DISCUSSION

In the present study, we showed that the DEMMI is a feasible, reliable, and moderately valid instrument with minimal floor or ceiling effects to measure mobility within the ICF activity domain in patients who are critically ill in the ICU, M-ICU, and regular hospital ward. The intrarater and interrater reliability were high on all assessment occasions, and the validity of the DEMMI was shown by moderately convergent correlations with the Katz ADL, BI, and MMT and a low divergent correlation with the APACHE II. As a result, the DEMMI has shown good clinimetric properties to assess activity levels in patients who are critically ill.

Within the literature, other instruments for measuring ADL or mobility, such as the BI and the Katz ADL, have been shown to be reliable and valid.(2,14) However, they have the disadvantage of being multidimensional, including several items (eg, bladder, bowel) non relevant to patients within the ICU. These items are scored negatively during ICU stay, leading to a floor effect in the ICU. The Physical Function ICU Test short version (PFIT) and the FSS-ICU are recently developed instruments measuring unidimensional mobility in patients in the ICU.(12,13) The clinimetric properties of the PFIT have been studied, and the applicability in a population in the ICU was confirmed by Rasch modeling.(12,34) Nonetheless, it contains items that are too difficult for many patients in the ICU, resulting in notable floor effects in the ICU. The ceiling effects at discharge (20%) were probably caused by the highest-order item of the PFIT (ie, marching), whereas other higher-order tasks (eg, walking away from the bed) were possibly needed to realize a lower ceiling effect.(12) The FSS-ICU seems appropriate for the use in patients who are critically ill, as it includes relevant ICU functional tasks, such as rolling, supine-to-sit transfers, sitting at the edge of bed, and sit-to stand transfers. However, the reliability and validity of the FSS-ICU in an ICU setting and other settings have not been reported.(8,35)

Our results illustrate that the DEMMI does not share these limitations due to the range of items in the ICU or regular hospital wards. The DEMMI could be administered in all patients in the ICU and in patients at the regular hospital ward. Moreover, in a recent systematic review by Parry et al,(8) a schematic guide for the use of outcome measures for patients who are critically ill within the ICF framework was recommended. Based on the clinimetric properties in various populations outside the ICU, the DEMMI was proposed for the measurement of mobility after ICU discharge at the regular ward and after return to the community.(8) Our study showed good clinimetric properties and feasibility of the DEMMI when used in patients who are critically ill in the ICU and, therefore, should be considered as a standard clinimetric tool.

The clinimetric properties of the DEMMI found in the present study are similar to those found in previous studies. De Morton et al (17) found a reliability coefficient of .87 in a general medical population. Other research groups confirmed these results in a different general elderly population with knee or hip osteoarthritis.(18) The research group of de Morton et al (15) showed comparable results regarding the validity of the DEMMI, with a correlation of .68 with the BI, as well as regarding the divergent validity, showing a correlation of .07 with the APACHE II. The MDC_{90} in our study was lower than that reported by de Morton et al.(16)

Our study had some intrinsic limitations. Our results were based on a mixed patient group (n=115) with a mean APACHE II score of 15.2 at T0. This relatively low severity of illness score at ICU admission could be attributed to the large group of patients with elective surgery. In our sample, some of these patients developed severe complications, such as sepsis, acute respiratory distress syndrome, and multiple organ failure, regardless of the low APACHE II score at admission. These findings are illustrated by the calculated SOFA score, representing the severity of illness score for hospital mortality and morbidity (mean=7, SD=3.6). In calculating the interrater and intrarater reliability, the study sample size (n=115) is comparable to that of other reliability studies of the DEMMI.(15–17) To improve the generalizability of our study, increasing the sample size and inclusion of multiple ICU hospitals and other clinical wards would have been preferable.

Another consideration in this study was that physical assessment in patients in the ICU is complicated due to critical pulmonary and hemodynamic conditions necessitating medication and invasive equipment. In addition, due to critical illness, this medical situation might change rapidly.(36) This factor might have biased the results with respect to the intrarater reliability. We found that the intrarater reliability was lower than the interrater reliability. This finding also might have been the cause of a relatively low ICC of the intrarater reliability below .9 at T0, as these measurements were performed within 1 hour due to the fact that the DEMMI should be administered in total at the same time. In this critically ill population, it is expected that the ability to perform mobility activities will change within an hour due to fatigue and exertion. Another limitation is that we did not determine the intrarater reliability at T1 because we anticipated practical feasibility issues for the repeated measurements in patients on the regular ward. Based on a previous study by de Morton et al (17) showing high intrarater reliability (Pearson r=.86) in elderly patients with frailty at a hospital ward, we assumed high intrarater reliability on the regular ward because of the stabilized pulmonary and hemodynamic conditions of the patients compared with the ICU situation. Finally, this study could be criticized for the loss to follow-up, primarily due to early hospital discharge or mortality (Fig. 1). We do

not think that the loss to follow-up biased our results because the remaining sample size retained sufficient power to perform the analysis.

The DEMMI provides the physical therapist with accurate and reliable information on the level of mobility in patients in the ICU. Its clinimetric properties and the range of items indicate that the DEMMI is a clinically feasible instrument. Due to minimal floor or ceiling effects, it has great potential to be used throughout the rehabilitation process of patients who are critically ill.

The ICU health care team, therefore, should recommend measuring the functional status of patients in the ICU at each stage of critical illness within the ICU and hospital regular wards until discharge. Further research is indicated to evaluate the hierarchical structure of the mobility items in the DEMMI in an ICU population.

AUTHORS' CONTRIBUTIONS

Mrs Sommers, Mr Vredeveld, Dr Engelbert, and Dr van der Schaaf provided concept/ idea/ research design. All authors provided writing. Mrs Sommers and Mr Vredeveld provided data collection. Mrs Sommers, Mr Vredeveld, Mr Lindeboom, Dr Engelbert, and Dr van der Schaaf provided data analysis. Dr Engelbert and Dr van der Schaaf provided project management. Dr van der Schaaf provided fund procurement and institutional liaisons. Mr Lindeboom, Dr Engelbert, and Dr van der Schaaf provided consultation (including review of manuscript before submission). The authors thank physical therapists Robin Kwakman, Denise Wieferink, Daniela Dettling, Dennis Gommers, and Tineke van Heuveln for their comprehensive guidance of patients during the data collection of this study.

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APPENDIX.

Summary of Contraindications for Physical Therapy(21)[a]

* Heart rate
  - Recent myocardial ischemia
  - Heart rate frequency < 40 or > 130 beats per minute
* Blood pressure
  - MAP < 60 mm Hg or > 110 mm Hg
* Oxygen saturation
  - $SpO_2 \leq 90\%$
* Mechanical ventilation
  - $FIO_2 \geq 0.6$ (60%)
  - PEEP ≥ 10 cm H_2O
* Respiratory frequency
  - Frequency > 40 breaths per minute
* Level of consciousness
  - RASS score -4, -5, 3, or 4
* Inotropic support
  - Doses of dopamine ≥ 10 mcg/kg/min
  - Doses of noradrenaline ≥ 0.1 mcg/kg/min
* Temperature
  - ≥ 38.5°C
  - ≤ 36°C
* Other
  - Clinical expertise (ie, sweating, abnormal face color, pain, fatigue)
  - Surgical contraindications (ie, unstable fractures, open abdomen)
  - Presence of lines that impede mobilization (eg, left ventricular assist device, intra-articular balloon pump)
  - Neurological instable: ICP ≥ 20 cm H_2O

[a] MAP = mean arterial pressure, SpO_2 = oxygen saturation, FIO_2 = fractional concentration of inspired oxygen, PEEP = positive end expiratory pressure, RASS = Richmond Agitation Sedation Scale, ICP = intracranial pressure.

CHAPTER 4

Feasibility of exercise testing in patients who are critically ill: a prospective, observational multicenter study

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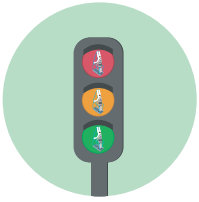

ABSTRACT

Objective: To evaluate the feasibility and safety of exercise testing and to describe the physiological response to exercise of patients in the Intensive Care Unit (ICU).

Design: A prospective observational multicenter study.

Setting: Two mixed medical-surgical ICUs.

Participants: Patients (N= 37; with no primary neurological disorders, 59% men; median age 50 y; ICU length of stay 14.5 d; Acute Physiology and Chronic Health Evaluation IV 73.0) who had been mechanically ventilated for more than 48 hours and were hemodynamically stable enough to perform physical exercise.

Interventions: A passive or active incremental exercise test, depending on muscle strength, on a bed-based cycle ergometer.

Main outcome measures: Feasibility and safety were evaluated based on protocol adherence and adverse events. Physiological responses to exercise quantified as changes in respiratory frequency (RF), oxygen uptake (VO_2), carbon dioxide output (VCO_2), respiratory exchange ratio (RER), and blood lactate.

Results: Thirty-seven patients of whom 18 were mechanically ventilated underwent the exercise test. The active incremental test was performed by 28, and the passive test by 9 participants. Thirty-three (89%) accomplished the test according to the protocol and 1 moderate severe adverse event (bradycardia; heart rate 44) occurred shortly after the test. RF, VO_2 , VCO_2 and lactate increased significantly, whereas RER did not change during the active incremental exercise test. No changes were observed during the passive exercise test.

Conclusions: It is safe and feasible to perform exercise testing on a bed-based cycle ergometer in patients who are critically ill and a physiological response could be measured. Future research should investigate the clinical value of exercise testing in daily ICU practice and whether exercise capacity and its limiting factors could be determined by incremental exercise testing.

Critical illness is associated with long-term physical impairments with intensive care unit -acquired weakness (ICU-AW) and reduced exercise capacity as most commonly observed manifestations.(1-8) Early rehabilitation of patients within the intensive care unit (ICU) has been advocated to prevent physical deterioration, but knowledge on how to determine the optimal training load in patients who are critically ill is lacking.(9-14) To improve cardiorespiratory fitness, training load should be sufficient. However, exercise should be safe, and overload should be avoided in critically ill patients with low exercise tolerance due to their critical illness. In healthy persons, cardiopulmonary exercise testing is considered the criterion standard to determine exercise capacity and is used to prescribe exercise intensity and to evaluate exercise programs.(15-19)

To our knowledge, incremental exercise testing in an ICU setting has not been described and ergometers to perform a cardiopulmonary exercise test, enabling very low resistance and a fixed workload for the use in weakened critically ill patients in an ICU are not available. Moreover,(20-22) in view of the hemodynamic, respiratory, metabolic and musculoskeletal changes encountered during critical illness (23), it is unknown how patients who are critically ill respond to exercise.(16)

As a first step towards the development of a method for quantifying exercise capacity in an ICU population, the aim of this study was to evaluate the feasibility and safety of exercise testing and to describe the physiological responses to exercise in critically ill patients in the ICU.

METHODS

We conducted a prospective, observational, 2-center study in the mixed medical-surgical ICUs in the Netherlands. Inclusion of patients was from September 2014 to July 2015. The study protocol was submitted to the Medical Ethics Review Committee as an observational study during physiotherapy treatment in which increasing bed-based cycling was provided and cardiorespiratory parameters were measured. The Ethical Review Board of the Amsterdam UMC, (AMC) waived the request for ethical approval as the Medical Research Involving Human Subjects Act did not apply to the study.

Surgical and medical adult patients in the ICU who had been mechanically ventilated for more than 48 hours (or were extubated after > 48 h but still in the ICU), who were able to cycle (ie, no physical limitations such as lower extremity amputee or fracture or cognitive impairments) were eligible for the study. Patients with neurological disorder as primary reason for admission to the ICU (ie, subarachnoid bleeding, stroke, traumatic brain injury, neuromuscular disease, etc) were not screened for eligibility. Exclusion criteria included contraindications to perform physical exercise safely according to the criteria of the Evidence Statement for Physiotherapy in the ICU (appendix 1),(14), unable

to follow instructions (measured with the Standardized 5 Questions < 3),(24-26) and insufficient knowledge of the Dutch language. Patients who were extubated and breathing spontaneously with oxygen (O_2) supplementation were also excluded because metabolic factors cannot be measured due to O_2 in the canopy system.(27)

Protocol exercise test

Before starting the exercise test, muscle strength of hip flexion, knee extension and ankle dorsiflexion were assessed according to the Medical Research Council (MRC). Patients with a lower leg muscle strength MRC < 3 (unable to move against gravity) were assigned to the passive protocol, and patients with an MRC ≥ 3 (active movement possible against gravity) were assigned to the active incremental test protocol.

The calibrated Quark RMR ICU[a] was used to assess gas exchange 10 minutes before, during, and 10 minutes after the test in patients who were mechanically ventilated. In patients who were nonventilated, the canopy system, consisting of a transparent hood connected to a blower box moving air in and out, was used.

The test was performed in a semi-recumbent position on a bed-based cycle ergometer[b] (a motor-assisted therapy device).(28) The active cycling protocol consisted of a (sub) maximal, symptom-limited incremental test. After 1 minute of unloaded cycling (no resistance) at 20 revolutions per minute (RPM), each minute the resistance was increased by 1 step. As the ergometer did not display the actual workload, the resistance was increased in fixed steps in accordance to the settings of the ergometer. The passive protocol consisted of unloaded cycling in a semi-recumbent position. The passive cycling protocol consisted of 20 minutes of continuous passive exercise performed with the cycle ergometer at a fixed velocity of 20 RPM.

The (active and the passive) test was terminated if the respiratory exchange ratio (RER) exceeded 1.10, the heart rate exceeded 80% of the maximum predicted heart rate (Fox formula: 220-age), the RPM decreased to < 10 per minute, when patient safety was threatened according to the safety criteria (see appendix 1), or the participant was unable to continue the test for any other reason.(9, 14, 28, 29)

Measurements

The feasibility of the exercise test was evaluated according to (1) the applicability of the protocol; (2) reasons why the test could not be performed; (3) reasons for early termination of the test; (4) the number of adverse events that occurred during and within 10 minutes after the exercise test. The adverse events were graded as mild, moderate, severe, life-threatening, or disabling and death-related adverse events according to the Common Terminology Criteria for Adverse Events.(30)

To evaluate the physiological responses, the following parameters were recorded from the Quark RMR: oxygen uptake (VO_2 [mL/min]), carbon dioxide output (VCO_2 [mL/min]) and the RER (ratio VCO_2/VO_2) adjusted to height and weight. Before, during and after the test, hemodynamic parameters (heart rate, blood pressure (systolic blood pressure [SBP][mmHg]/ diastolic blood pressure [mmHg]/ mean arterial pressure [mmHg])) and respiratory parameters (oxygen saturation and respiratory frequency [RF]) were recorded. In patients with an arterial line, blood lactate (mmol/L) levels were collected before and directly after the test. Physiological outcomes were measured 5 minutes before the test to obtain baseline physiological parameters during rest.

The 6-to-20 Borg ratings of perceived exertion scale (31) and muscle fatigue (yes/no) were obtained directly after the test to quantify fatigue and the intensity of exercise. After the test, patients were monitored for 10 minutes to record changes in VO_2 and heart rate.(20, 21, 30) Data of maximal workload (watt), duration of (active and passive) cycling (min), resistance, and RPM were obtained from the cycle ergometer after each test.

The following data were obtained from the patients' medical records: age, sex, height, weight, length of ICU stay, diagnosis on admission to the ICU, severity of disease according to the Acute Physiology and Chronic Health Evaluation IV,(32) duration of mechanical ventilation, ventilation parameters at the moment of testing and the muscle strength expressed as the MRC sum score. The MRC sum score for the assessment of ICU-AW is defined as the total score obtained from the bilateral testing of 6 muscle groups (abduction of the shoulders, flexion of the elbows, extension of the wrists, flexion of the hips, extension of the knees, and dorsal flexion of the feet).(1, 33) The minimal score for each muscle is 0, indicating no muscular contraction, and the maximum score is 5, indicating normal muscle strength. This leads to a range for the MRC sum score of 0 to 60 points. A score < 48 indicates ICU-AW.(34)

Statistical analysis

Continuous variables are presented as the means and standard deviations or, in the case of a skewed distribution, as medians with the interquartile range (IQR) (25th – 75th percentile). Normality was checked using the Kolmogorov– Smirnov test. Categorical variables were expressed as proportions with percentages. The metabolic parameters were analyzed using 10-second average samples to minimalize the effects of the breath-by-breath signal noise.(35) The peak VO_2 was defined as the average VO_2 during the final 30 seconds of exercise. The physiological response and the metabolic parameters between baseline and the peak were examined using the paired samples *t* test by a normal distribution, whereas in the case of a skewed distribution, the Wilcoxon signed-ranked was used. Statistical significance was indicated by a *P* value less than .05. Statistical analyses were performed using SPSS software version 22.0.[c]

RESULTS

During the recruitment period, 179 patients were screened for eligibility in both centers, and 39 patients met the inclusion criteria. Reasons for exclusion included:

- Spontaneous breathing with oxygen supplementation (35.2%). Patients who were extubated and breathing spontaneously with oxygen (O_2) supplementation were excluded because metabolic factors cannot be measured due to O_2 in the canopy system.(27)
- Not meeting the safety criteria for performing physical exercise (19.6%).
- Unable to follow instructions (7.3%) and discharge to another department in the weekend / or discharge to another hospital before screening for eligibility (8.4%) (fig 1).

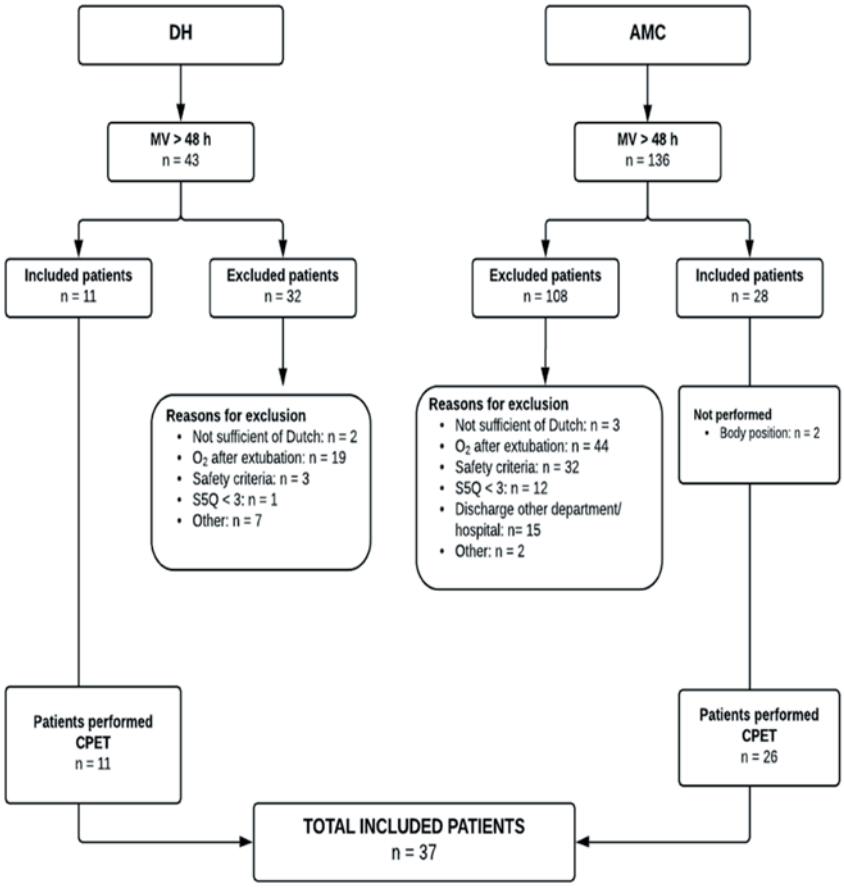

Figure 1 Flow diagram of the study participants in both centers

Abbreviations AMC, Amsterdam UMC (location AMC); CPET, cardiopulmonary exercise testing; DH, Deventer Hospital; MV, mechanical ventilation; S5Q, Standardized 5 Questions.

Patient characteristics at enrollment are presented in table 1. Twenty-eight patients (75.7%) performed the active test protocol of whom 11 were mechanically ventilated. Nine patients (24.3%) performed the passive cycling test protocol of whom 7 were mechanically ventilated (see table 1). Median MRC muscle strength was 41 (IQR 32-47), and 76% had ICU-AW (MRC sum score < 48). The median duration of the active test was 6.1 minutes (IQR 4.3-8.7), with a median RPM of 36 (IQR 27-43) and a median of the maximum workload of 5.0 watts (IQR 2.5-9.5). The median duration of the passive test was 15.0 minutes (IQR 10.3-20) with 20 RPM.

Table 1 Characteristics of patients at moment of testing

Characteristic	Patients (n = 37)		Passive cycling (n=9)		Active cycling (n=28)	
Sex, male, n (%)	22	(59.5)	5	(55.6)	17	(60.7)
Age, y *	61.3	(50.0–75.5)	68	(54.5-76.5)	62.5	(50-74.3)
Admission diagnosis, n (%)						
- Medical	17	(45.9)	5	(55.6)	12	(42.9)
• Pneumonia	8	(21.6)	4	(44.4)	4	(14.3)
• Sepsis	5	(13.5)	0		5	(17.9)
• Reanimation	4	(10.8)	1	(11.1)	3	(10.3)
- Emergency surgery	11	(29.7)	3	(33.3)	8	(28.6)
• Stomach	7	(18.9)	3	(33.3)	4	(14.3)
• Thorax	2	(5.4)	0		2	(7.1)
- Planned surgery	9	(24.3)	1	(11.1)	8	(28.6)
• Stomach	3	(8.1)	0		3	(10.3)
• Thorax	6	(16.2)	1	(11.1)	5	(17.9)
ICU stay to inclusion (d) *	14.5	(8.0-21.8)	9	(8-12.8)	16.5	(9.5-25.8)
Mechanical ventilation to inclusion (d)*	11.0	(6.5-14.5)	9	(7.3-12.8)	11	(5.5-16.5)
Respiratory parameters						
Mechanical ventilation, n (%)	18	(48.6)	7	(77.8)	11	(39.3)
With tracheostomy, n (%)	4	(22.2)	0	(0)	4	(36.4)
Non mechanical ventilation, n (%)	19	(51.4)	2	(22.2)	17	(60.7)
Severity of illness						
APACHE IV *	73.0	(60.0- 104.0)	81	(66-116.5)	69.5	(58.3-102.5)
Physical function						
Muscle strength sum score (MRC scale, 0-60) *	41	(32-47)	30	(10.5-34)	42.5	(38.3-48.8)

Abbreviations; APACHE, Acute Physiology and Chronic Health Evaluation Score.
* Shown in median (IQR)

Feasibility

The exercise test was performed by one physiotherapist and took 60 minutes in total to perform, including calibration, preparation and cleaning of the materials after finishing

the test procedure. Of the 39 patients meeting the inclusion criteria, 2 could not adopt the required body position due to dyspnea and a rectal drain and could therefore not perform the test (see fig 1). Consequently, 37 (94.9%) patients performed the test. In 4 (1 passive and 3 active protocol) (10.8%) cases, the test could not be completed due to increasing pain. However, data of these patients until termination of the test were included in the analysis (table 2).

In 6 (active protocol) (16.2%) patients, the canopy had to be removed after the exercise test during the recovery period because of perceived dyspnea.

One adverse event with bradycardia (HR 44 beats/min (BPM)) was reported 4 minutes after the test was performed. The bradycardia resolved after adjustments to medication and was considered “moderate”.

Physiological response

The physiological responses for all parameters during the active and passive test are presented in table 2.

Respiratory and metabolic response

During peak exercise in the active cycling test, the median RF, VO_2 and VCO_2 increased significantly, from 20 breaths/min (IQR 15-23) to 24 breaths/min (IQR 20-28) (P = .001); the VO_2 increased from 291 mL/min (IQR 213-385) to 384 mL/min (IQR 269-497) (P < .001) and the VCO_2 increased from 217 mL/min (IQR 179-275) to 279 mL/min (IQR 201-395) (P < .001). There was no change in the RER (see table 2).

In the patients who performed the passive cycling test protocol, the median RF, VO_2, VCO_2 and RER values did not change during cycling (see table 2).

Cardiovascular response

During the active cycling protocol, heart rate and SBP increased significantly from rest to peak exercise, from 86 BPM (IQR 76-98) to 93 BPM (IQR 79-110) (P < .001) and from 133 mmHg (IQR117-154) to 143 mmHg (IQR129-164) (P = .003). The median time to heart rate recovery was 60 seconds (IQR 0-480).

In the patients who performed passive cycling, no significant changes in heart rate and SBP were observed (see table 2).

Peripheral musculoskeletal response

In patients performing the active exercise test, the median Borg score was 13 (IQR 11-14) at peak exercise, and 17 patients (61%) reported muscle fatigue after the test.

Lactate levels increased significantly (mmol/L) (1.1 [IQR 0.7-1.8] vs. 1.6 [IQR 0.9-2.0]; P=.005) directly after peak exercise (see table 2).

Table 2 Physiological response to exercise test

Physiological response	Active cycling (*n* = 28)			Passive cycling (*n* = 9)		
	REST	PEAK	DIFFERENCE	REST	PEAK	DIFFERENCE
Respiratory response*						
SpO_2 (%)	97 (95–99)	97 (95–99)	0 (-1–1)	98 (94–98)	97 (95–98)	0 (-3 to 2)
RF(breaths/min)	20 (15–23)	24 (20–28)	5 (1–9)†	25 (20–29)	25 (21–34)	1 (-4 to 9)
VO_2 (mL/min)	291 (213–385)	384 (269–497)	82 (32–173)†	259 (240–323)	344 (242–386)	50.2 (-9 to 99)
VCO_2 (mL/min)	217 (179–275)	279 (201–395)	61 (6–117)†	200 (188–282)	226 (198–322)	12.3 (-16 to 46)
Peak VO_2 (mL/kg/min)		5.1(3.6 – 7.1)			4.2 (3.3–4.5)	
RER	0.78 (0.69–0.91)	0.77 (0.69–0.91)	-0.01 (-0.07–0.05)	0.79 (0.76–0.87)	0.79 (0.67–0.89)	-0.04 (-0.06 to 0.04)
Cardiovascular response*						
HR (beats/min)	86 (76–98)	93 (79–110)	7 (3–13)†	89 (85–95)	91 (84–98)	2 (-3 to 5)
SBP (mmHg)	133 (117-154)	143 (129–164)	5 (0–16)†	114 (93–165)	115 (105–159)	1 (-5 to 12)
Blood analyses*						
Lactate (mmol/L)	1.1 (0.7–1.8)	1.6 (0.9–2.0)	0.2 (0.0–0.4)†	1.4 (0.6–3.1)	1.5 (0.6–2.7)	-0.1 (-0.3 to 0.1)

Abbreviations: HR, heart rate; SpO_2, oxygen saturation.
* Shown in median (IQR)
† significant $p < .05$.

Patients performing the passive test protocol had a median Borg score of 14 (IQR 11-15). Three (33%) patients reported fatigue as the reason for termination the passive test.

No changes in lactate and glucose levels were observed in patients who completed the passive exercise test.

DISCUSSION

This feasibility study showed that incremental exercise testing with a bed-based cycle ergometer can be performed safely in a critically ill population in an ICU. Moreover, we demonstrated that a physiological response to incremental exercise could be evoked, and changes in physiological parameters could be monitored.

Our study population consisted of patients who had been mechanically ventilated for at least 48 hours, had been treated in the ICU for (median) 14.5 days and for whom it was considered safe to perform physical exercise.(14) Ninety percent of these patients were able to accomplish the exercise test and no severe adverse events occurred. (16, 18, 31, 35-37)

Based on previous research, it was assumed that responses to exercise in patients who are critically ill would differ from healthy subjects and do not correlate with the severity of effort necessary to perform the exercise.(38) Moreover, previous research demonstrated increased energy expenditure, cardiac output and resting heart rate, indicating a low exercise tolerance as a consequence of the metabolic response to stress in patients who were critically ill.(23, 39, 40) In agreement with the literature, we observed a relatively small increase in physiological parameters from rest to peak exercise.(16, 35) With regard to the very low maximum workload during the active exercise test (median 5.0 watts [IQR 2.5-9.5]) and the high level of perceived exertion (Borg scale 13 [IQR 11-14]), we conclude that the ability of our population to tolerate exercise was very low. For clinical practice this implicates that one should be aware of the risks of overload in performing exercise with patients who are critically ill.

Considering the high incidence of ICU-AW, we speculate that the peripheral musculoskeletal system with limited maximum VO_2 might have played an important role in the limited exercise performance in our study population.

Research on the cardiopulmonary response to exercise in patients who are critically ill is limited; only 3 studies (20-22) have previously described the response to exercise using gas exchange measurements in patients in the ICU. Collings et al (22) observed significant increases in the VO_2, VCO_2, minute ventilation, mean arterial pressure and heart rate during transfer between the bed and the chair. Camargo Pires-Neto et al (20) demonstrated that early (<72h after ICU admission) continuous passive cycling in patients who were deeply sedated and mechanically ventilated is feasible and can be performed safely. Hickmann

et al (21) observed a higher-than-expected energy expenditure in patients who cycled actively for 30 minutes at a fixed resistance in a sitting position. In patients who were sedated, no physiological changes in response to passive cycling were found.

The findings of our study, along with the scarce available literature of responses to exercise in patients who are critically ill, do not yet allow the drawing of firm conclusions regarding the clinical value of the changes in physiological parameters that were observed. Future research should investigate the clinical interpretation of physiological changes during exercise in patients who are critically ill based on the effect size and minimal clinically important difference, as well as in comparison with healthy subjects in similar test situations.

Study Limitations

A weakness of this study, potentially limiting the generalizability of the results, is the strict inclusion criteria, which resulted in a small number (< 22%) of the screened patients being eligible for the study. We chose to include patients who had been mechanically ventilated for more than 48 hours, as this population is considered at high risk for ICU-AW with physical decline and are therefore most likely in the need for a personalized rehabilitation program.(7, 41) For safety reasons, we a priori excluded patients who did not fulfill the safety criteria for performing exercise. In addition, a large proportion of the eligible patients (35.2%) could not be included, because a canopy system is not able to measure O_2 uptake in patients with O_2 supplementation.(27) Also, patients with primary neurological disorders were not included. Consequently, the criteria used in this study led to a homogeneous study population in the ICU of medical and surgical patients with a prolonged ICU stay. Moreover, as our patients were included in a university and in a community hospital, this seems to be a representative ICU population for whom it is safe to exercise and who could benefit from a tailored exercise program.

Another limitation is the small group of patients that cycled passively. Only 9 patients were included, of whom 8 patients completed the test. Despite the small number of patients that performed the passive test, the finding that passive exercise seems not to evoke physiological changes might have important clinical implications with respect to prescribing (passive) exercise in patients who are critically ill. Several studies reported on the benefits of passive cycling in ICU populations due to changes in inflammatory cytokines that limit muscle wasting.(9, 42-46) Our findings suggest that passive cycling, for instance to prevent muscle wasting, might be applied safely in patients with critical illness and hemodynamic instability.

Another limitation is that the actual workload delivered in watts during each step increment of the active protocol could not be derived during the test with the ergometer that was used in this study. Although we used a protocol in which the resistance was

increased in similar steps for all participants, the clinical interpretation of the observed physiological response remains difficult. Yet, the bed-based cycle ergometer provided detailed data of the average and maximum workload (wattage) after completion of the exercise test. With respect to the limitation of the bed-based cycle ergometer, it was preferred for this study because it has been recommended for the use of daily exercise in patients in the ICU.(9)

Another limitation is that the interpretation of the relative small changes in respiratory and metabolic parameters is difficult since the minimal clinically important difference is not available.

To develop a valid incremental exercise test for quantifying exercise capacity in patients who are critically ill, a bed-based cycle ergometer enabling very low workload and a display of actual workload in wattage is a prerequisite. With such a test, a next step would be to investigate the association between energy expenditure and workload, to detect clinically meaningful changes in patients with metabolic disturbances, and to compare these data with those of healthy subjects.

Also, the role of potential limiting factors from the metabolic system, the peripheral musculoskeletal system and cardiorespiratory function in exercise performance in critically ill patients should be investigated.

CONCLUSION

We found that incremental exercise testing could be applied safely in patients in the ICU who were critically ill, mechanically ventilated, and physiologically stable. Similar to healthy subjects, an exercise test with an incremental resistance protocol induced a measurable physiological response in patients who are critically ill. Future research should investigate the value of the clinical application of incremental exercise testing in daily ICU practice for assessing the integrated physiologic response to exercise and the relative contributions of cardiac, respiratory, and musculoskeletal impairment to exercise capacity.

SUPPLIERS

a. Quark RMR ICU: COSMED, The Metabolic Company.
b. MOTOmed letto2: RECK-Technik.
c. SPSS software version. 22.0: IBM Corporation

LIST OF ABBREVIATIONS

ICU	intensive care unit
ICU-AW	intensive care unit - acquired weakness
IQR	interquartile range
MRC	Medical Research Council
O_2	oxygen
RER	respiratory exchange ratio
RF	respiratory frequency
RPM	revolutions per minute
SBP	systolic blood pressure
SpO_2	oxygen saturation
VCO_2	carbon dioxide output
VO_2	oxygen uptake

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APPENDIX

Appendix 1 Contra-indications for Physical Therapy Treatment

- Heart rate
  - Recent myocardial ischemia
  - Heart frequency < 40 or > 130 beats/min
- Blood pressure
  - MAP < 60 mmHg or > 110 mmHg
- Oxygen saturation
  - $SpO_2 \leq 90\%$
- Mechanical ventilation
  - $FiO_2 \geq 0.6$ (60%)
  - PEEP ≥ 10 cm H_2O
- Respiratory frequency
  - Frequency > 40 breaths/min
- Level of consciousness
  - RASS score -4, -5, 3 or 4
- Inotropic support
  - Doses of dopamine ≥ 10 mcg/kg/min
  - Doses of noradrenaline ≥ 0.1 mcg/kg/min
- Temperature
  - ≥ 38.5°C
  - ≤ 36°C
- Other
  - Clinical expertise (sweating, abnormal face color, pain, fatigue)
  - Surgical contra-indications (i.e. unstable fractures, open abdomen)
  - Presence of lines that make mobilization unsafe
  - Neurologically instability: ICP ≥ 20 cmH_2O
- Patients were excluded if 1 or more of these criteria were met.

Abbreviations: FiO_2, fractional concentration of inspired oxygen; ICP, intra cranial pressure; MAP, mean arterial pressure; PEEP, positve end expiratory pressure; RASS, Richmond Agitation Sedation Scale; SpO_2, oxygen saturation.

CHAPTER 5

Feasibility of muscle activity assessment with surface electromyography during bed cycling exercise in Intensive Care Units patients

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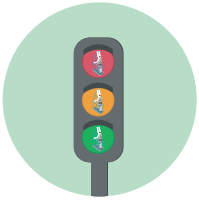

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ABSTRACT

Introduction: Intensive Care Unit (ICU) patients often develop weakness. Rehabilitation is initiated early to prevent physical deterioration, but knowledge of optimal training schedules is lacking. A reliable method to assess muscle activity during exercise is needed. In this study we explored the feasibility of electrical activity measurement by surface electromyography (sEMG) during bed cycling in ICU patients.

Methods: sEMG was performed in 9 ICU patients and 6 healthy controls. A standardized 1-minute incremental resistance bedside cycle ergometer protocol was used.

Results: The median cycle time was 5.3 minutes in patients and 12.0 minutes in controls. The maximum sEMG increased in both groups; the minimal sEMG activity remained the same in patients, whereas an increase in the control group was found.

Discussion: sEMG is feasible and can detect muscle activity during bed cycling in ICU patients. It may be a useful monitoring tool. Repeated measurements could possibly provide information on the effects of training.

In critically ill patients who are admitted to the intensive care unit (ICU), muscle weakness often develops, which is referred to as ICU-acquired weakness (ICU-AW).(1) Limiting bed rest and inactivity in early rehabilitation has a positive effect on muscle strength, walking ability and functional outcome.(2, 3) However, the optimal frequency, intensity and type of exercise for ICU patients is unknown.(3, 4)

To achieve training effects on muscle strength and cardiorespiratory fitness, the training load should be sufficient, but not excessive for the cardiac, respiratory and musculoskeletal systems. Monitoring of these systems during exercise is required to investigate and document the training intensity.(5) Therefore, a tool to assess muscle activity during exercise would be helpful to identify the optimal level of exercise intensity for an individual. Such information would allow the development of a personalized training schedule. Surface electromyography (sEMG) monitoring of muscle activity has been described in healthy volunteers to assess muscle activity and fatigue during exercise. (6-9) sEMG detects the electrical activity of the motor units that are involved in muscle contractions and can be considered a surrogate measure of the effort of the muscles. sEMG has been used for diaphragm monitoring in (mechanical ventilated) pre-term infants (10, 11), but monitoring of leg muscles during bed cycling in patients in the ICU is new and could provide useful information.

The aim of this pilot study was to determine whether sEMG is a feasible method for muscle monitoring during bed cycling in ICU patients.

METHODS

Between January 2015 and March 2016, we conducted a prospective pilot study in the ICU of the Academic Medical Center, Amsterdam, The Netherlands, a 34-bed, mixed medical-surgical ICU and medium care unit. The study was approved by the medical ethics review committee (NL50006.018.14), and informed consent from each study subject was obtained.

Adult ICU patients mechanically ventilated for > 48 hours who could cycle were eligible for the study. To enable active bed cycling, a muscle strength score ≥ 3 on the Medical Research Council (MRC) score for the legs (hip flexion, knee extension and dorsal flexion of the feet) was required. Exclusion criteria were contraindications to perform physical exercise according to the safety criteria of the Evidence Statement for Physiotherapy in the ICU (4), a score of < 3 (as measured using the Short 5-item Questionnaire [S5Q]) for inability to follow instructions (12-14), and insufficient knowledge of Dutch. The control group consisted of healthy subjects.

Measurements

The patients and controls were tested once. They were placed in the semi-recumbent position in bed with both legs placed in a motorized cycling exercise device (MOTOmed letto2; RECK-Technik, Betzenweiler, Germany). The cycling protocol started with 1 minute of passive, unloaded cycling at 20 revolutions per minute (RPM). Next, active cycling started, in which the resistance was gradually increased according to the fixed levels of resistance (steps) of the bed cycle. The capacity of the bed cycle consisted of 20 increasing levels of resistance with the lowest resistance at 0 (step 0). Resistance was increased at 1 step per minute in the patient group and 2 steps per minute in the control group, leading to a total protocol duration of 22 minutes and 12 minutes, respectively. The bed cycle provided detailed data of the maximal workload (watts), duration of cycling (minutes) and RPM. When RPM was reduced to < 10, the cycling was stopped. Throughout the exercise test, hemodynamic parameters (heart rate [HR], mean arterial pressure) and respiratory parameters (oxygen saturation and respiratory frequency) of the patients were collected to assess safety. When the HR was > 80% of the maximum predicted HR (using the Fox formula), or the patient's safety was threatened in any other way, the cycling was stopped. (2, 4, 15)

The Borg Rating of Perceived Exertion (RPE) scale (range 6-20 points) (16, 17) was used directly after the exercise. The Borg RPE scale is a reliable and valid measurement to assess exertion perceived by patients during and after the exercise,(18) with higher scores indicates higher perceived exertion.(17) Furthermore, the patients and controls were asked whether they experienced muscle fatigue (yes/no) in the legs. The sEMG (microvolts) recordings were performed using the Dipha-16 device (Inbiolab BV, Groningen, The Netherlands). Four electrodes (H59P Cloth Electrode; Kendall) were placed on the muscle rectus femoris in both legs (refer to Fig.S1 in Supplementary Material online). Without analog filtering, the sEMG data were digitized and sent wirelessly to the Dipha-16 system connected to a laptop with a Polybench (Applied Biosignals, Weener, Germany) application.

The following data were obtained from the patients' medical records: age; gender; reason for ICU admission; disease severity according to the Acute Physiology and Chronic Health Evaluation (APACHE) II (19); duration of mechanical ventilation and ICU stay at moment of testing; muscle strength (MRC sum score); and the level of mobility (on the testing day), as assessed by the de Morton Mobility Index (DEMMI). (20, 21) The APACHE score measures the severity of illness on ICU admission, with a range of 0 to 71. A higher score corresponds to more severe disease and a higher risk of death. The MRC sum score for the assessment of ICU-AW was defined as a score obtained from bilateral testing of 6 muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion).(22, 23) This leads to a range for the MRC sum score

of 0 to 60 points.(24) The DEMMI scale measures the full range of mobility within the ICF activity domain.(20, 21) It consists of 15 hierarchical mobility items (3 beds, 3 chairs, 4 static balances, 2 walking and 3 dynamic balance items). The score range is 0 to 100, where 0 represents poor mobility and 100 indicates high levels of independent mobility. From the control group, we obtained data on age, gender, Borg RPE scale and muscle fatigue.

Data and Statistical analysis

Patients' characteristics and continuous variables are described using descriptive statistics and are presented as the means and standard deviation or, in the case of a skewed distribution, as median and interquartile range (25th – 75th percentile, IQR). Normality was checked using the Kolmogorov–Smirnov test. Categorical variables are expressed as proportions with percentages.

The sEMG signals were transformed using root-mean-square (RMS) analysis, and the curves were analyzed offline in MATLAB (MATrix LABoratory, The Mathworks, Natick, Massachusetts).

Stable signals were selected from at least 10 cycling cycles immediately after an increase of resistance. The maximum sEMG (sEMGmax) and minimum sEMG (sEMGmin) were determined using a peak detection (high and low) algorithm in MATLAB. If peak detection identified 2 consecutive peaks or troughs, only the first peak or trough was used for the analysis.(11) From the selected 10 cycling cycles, the mean was calculated and used for group analyses.(11)

Three parameters, sEMGmax, sEMGmin and change in sEMG (ΔsEMG), were analyzed for each step.(7, 11) The peaks ($sEMG_{max}$) represent the number of motor units recruited during muscle contraction, and the troughs ($sEMG_{min}$) represent the number of motor units still active during relaxation of the muscle within each revolution cycle (see Fig. S2 in Supplementary Material online). By subtracting the troughs from the peaks, the ΔsEMG was calculated. *P* of < 0.05 for overall difference between groups (ICU patients and controls) was considered statistically significant using the linear mixed model.

RESULTS

Nine patients and 6 healthy volunteers were included in this pilot study. The reason for ICU admission were medical (4 patients), planned (3 patients), and unplanned surgical (2 patients). Further characteristics are presented in Table 1. The patients had decreased levels of physical function.

The patients cycled for a shorter duration than the healthy controls (see Table 2). The increase in resistance and maximal workload were lower. During the exercise test, there

were no changes in the hemodynamic and respiratory safety parameters monitored. Therefore, cycling was never stopped due to safety reasons. All controls completed the 12-minute program with 20 steps of increasing resistance.

Table 1 Patients characteristics at the moment of testing*

	ICU patients	Healthy persons
	(n = 9)	(n = 6)
Age, in years	70 (53-77)	59 (47-63)
Gender, women (n)	3	3
ICU stay to inclusion, in days	45 (14-59)	-
Patients with mechanical ventilation during measurement (n)	4	-
Mechanical ventilation, in days	18 (6-40)	-
APACHE II score	17.5 (14-21)	-
MRC-sumscore	42 (37-43)	60 (60-60)
DEMMI	24 (18-32)	100 (100-100)

IQR, interquartile range; ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation score; MRC: Medical Research Council scale; DEMMI: de Morton Mobility Index.
* Data presented as median (interquartile range), unless noted otherwise

Table 2 Results of bed cycling*

		ICU patients	Healthy persons
		(n = 9)	(n = 6)
Duration of the test (min:s)		5:3 (4:6-8:2)	12:0 (12:0-12:0)
Maximal workload (W)		3 (2.5- 5)	34.5 (32.5-54.5)
RPM		33.5 (26-38.3)	60 (53.3-73.8)
Maximal steps		4 (4-5)	20 (20-20)
Borg score		13 (12-15)	13 (9-13)
Reason to stop (n)	- Muscle fatigue	7	
	- Dyspnea	1	
	- Other	1	6 (End of program)

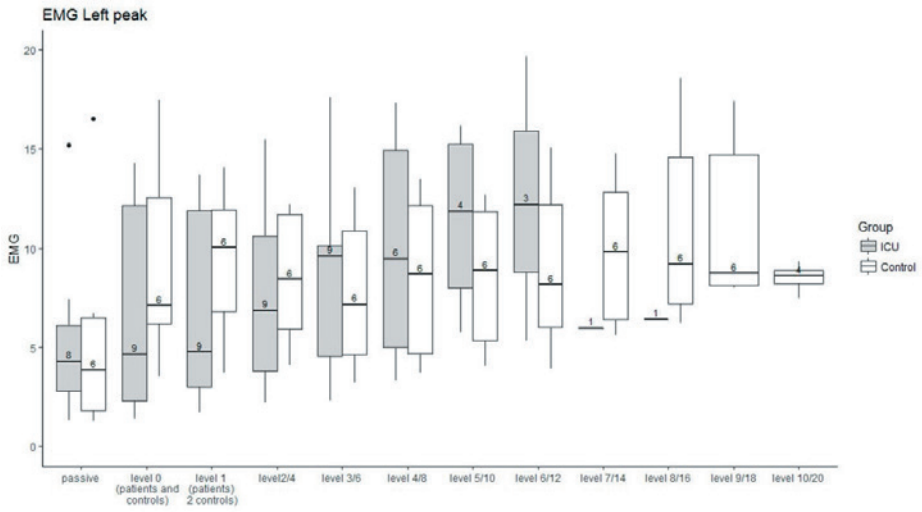
ICU, intensive care unit; RPM: revolutions per minute.
*Data presented as median (interquartile range), unless noted otherwise.

Surface Electromyography

At the start of cycling, during the passive period, sEMG activity was able to be recorded. Evaluation of sEMG during active cycling showed an increase in ΔsEMG in the ICU and control groups. This reflected primarily an increase in $sEMG_{max}$. The trough values ($sEMG_{min}$) showed no change in the patient group but an increase in the control group (Fig. 1).

The overall difference between the peaks ($sEMG_{max}$) of the ICU and control groups was not significant (0.27 µV [95% confidence interval -4.41 to 4.96]; *P* = 0.9). For trough ($sEMG_{min}$), a statistically significant difference of 1.8 µV (95% confidence interval: 0.05 to 3.53) was found (*P* = 0.047).

A.



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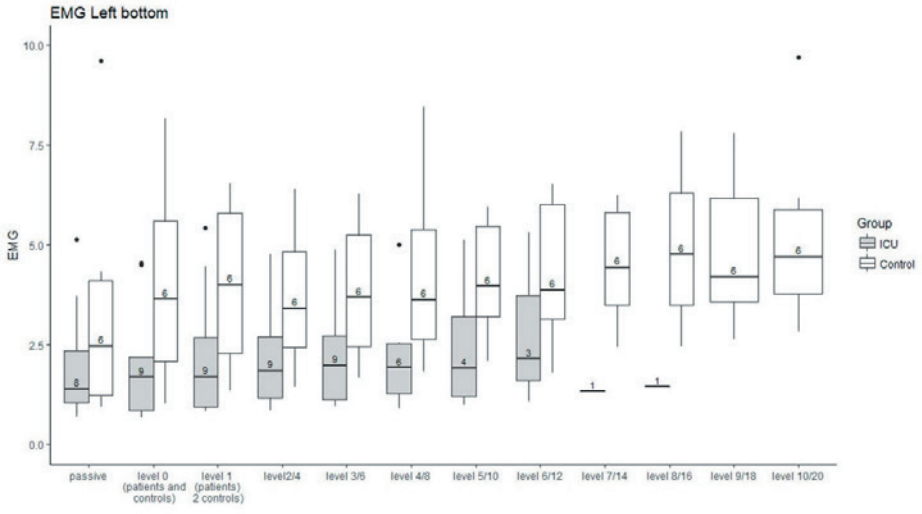

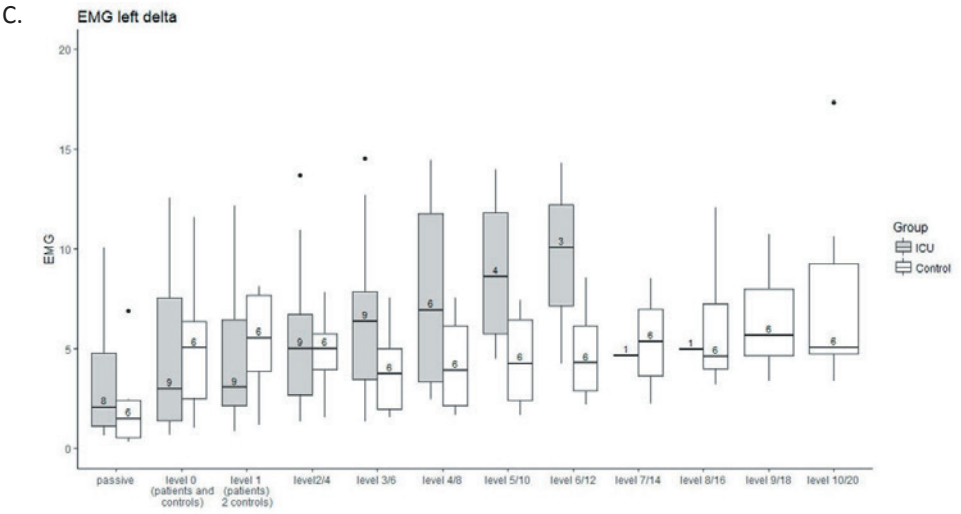

Figure 1 (A) Peak values ($sEMG_{max}$) from the patients in the ICU and controls. Numbers of participants are given on boxplot (EMG expressed in microvolts). Peak values of the left quadriceps are shown. **(B)** Trough values ($sEMG_{min}$) from patients in the ICU and controls. Numbers of participants are given on boxplot (EMG expressed in microvolts). Trough values of the left quadriceps are shown. **(C)** Delta values (ΔsEMG) from patients in the ICU and controls. Numbers of participants are given on boxplot (EMG expressed in microvolts). Delta values of the left quadriceps are shown.

DISCUSSION

In this pilot study we have shown that muscle activity from the rectus femoris can be monitored during bed cycling by sEMG in ICU patients. With increasing resistance, a clear increase in muscle activity was observed. These findings indicate that sEMG is feasible and may be useful to monitor muscle activity in ICU patients during exercise. In addition, during passive cycling, limited muscle activity was detected.

Recording of sEMG for the assessment of muscle activity during cycling in healthy persons has already been described.(6-9) In these populations, the method was found to be a useful tool to investigate muscle fatigue. sEMG during cycling was also used in patients with chronic low back pain or cerebral palsy to detect muscle activation and fatigue.(25, 26) Because all these studies were performed on normal training bikes instead of cycles used at the bedside, we decided to explore our method in healthy subjects to compare and validate our method of cycling in the ICU.

The methods used to analyze the results of sEMG recordings during cycling differ substantially in the literature.(6, 7) Martin-Valdez *et al*. and MacDonald *et al*. used the median frequency (MDF), muscle fiber conduction velocity (MFCV) and amplitude (RMS) to investigate muscle fatigue.(6, 7) Both studies recommended the use of RMS amplitude

as the most suitable and sensitive variable to observe muscle activity during incremental exercise and fatigue.(6, 7) In our pilot study, we evaluated the amplitude (in the RMS signal) found in 10 subsequent rotations directly after each increase in resistance. This straightforward method was also used to assess diaphragm weakness at our hospital.(11)

We also found sEMG activity in both groups during the passive period of cycling. This indicates that motor units were already activated in this phase. These results seem to support the observations by Kayambu *et al*. of the benefits of passive cycling in ICU populations. In those studies, they found that passive cycling reduced muscle wasting and prevented muscle atrophy, improved muscle strength and physical function and reduced length of hospital stay in medical and surgical ICU populations.(2, 27-29)

In most ICU patients, termination of bed cycling was caused by patients reporting muscle fatigue in the legs. None of the controls stopped for this reason. We also evaluated general exertion using the Borg RPE scale immediately after the exercise.(16, 17, 30) Both ICU patients and controls reported a Borg RPE score of 13 defined as “somewhat hard”, indicating that there was no difference in perceived exertion.(16, 17)

Limitations

Our study has some limitations that need to be acknowledged. Due to the strict inclusion criteria that we used, our study population was small and training was done at a rather late phase of the ICU admission. Another limitation of our study was the software of the bedside cycle ergometer used. The increased power during the test could not be set on a fixed wattage per minute. The software selected its own increase in resistance based on the RPM and steps algorithm of the bed cycle. Nevertheless, the bed cycle was preferred because it has been recommended and widely used in ICU patients for practical and safety reasons.(2) The program of the bed cycle provided detailed data of the wattage and number of RPMs after completion of the exercise. By following a strict protocol, we could increase the steps in a similar manner.

In conclusion, our pilot study has shown that sEMG is feasible and may be a useful monitoring tool to detect muscle activity during bed cycling in ICU patients. This investigation is a first step towards bedside monitoring of muscle exercise and fatigue in ICU patients during bed cycling. With multiple measurements in single patients over a longer period of time, more knowledge can be achieved on fatigue and training effects. Ideally, in such future projects, sEMG monitoring should be combined with oxygen uptake and heart rate measurements during incremental bed cycle exercises. Such studies could help to determine the optimal dose and timing of exercise for individual patients.

LIST OF ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
DEMMI	de Morton Mobility Index
HR	heart rate
ICU	intensive care unit
ICU-AW	ICU-acquired weakness
MRC	Medical Research Council
RMS	root mean square
RPE	rating of perceived exertion
RPM	revolutions per minute
sEMG	surface electromyography
S5Q	Short 5-item Questionnaire
$sEMG_{max}$	maximum sEMG
$sEMG_{min}$	minimum sEMG
ΔsEMG	change of the sEMG
MDF	median frequency
MFCV	muscle fiber conduction velocity

AUTHORS' CONTRIBUTIONS

J.S. designed the study, conducted the study, analyzed and interpreted the data, and drafted the manuscript.
M.vd.B. conducted the data analysis in MATLAB.
M. vd.S, F. N. and R.H.H.E. designed the study and reviewed the final version of the manuscript.
J.H. conceived the study, participated in its design and coordination, assisted in the data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

FUNDING

No funding was provided.

Procedures involving human and animal subjects
Ethics approval and consent to participate.
Ethical approval was obtained from the AMC local Ethics Committee (Amsterdam, the Netherlands; NL50006.018.14). Written informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

All data supporting the conclusions of this article are included in this article. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to disclose.

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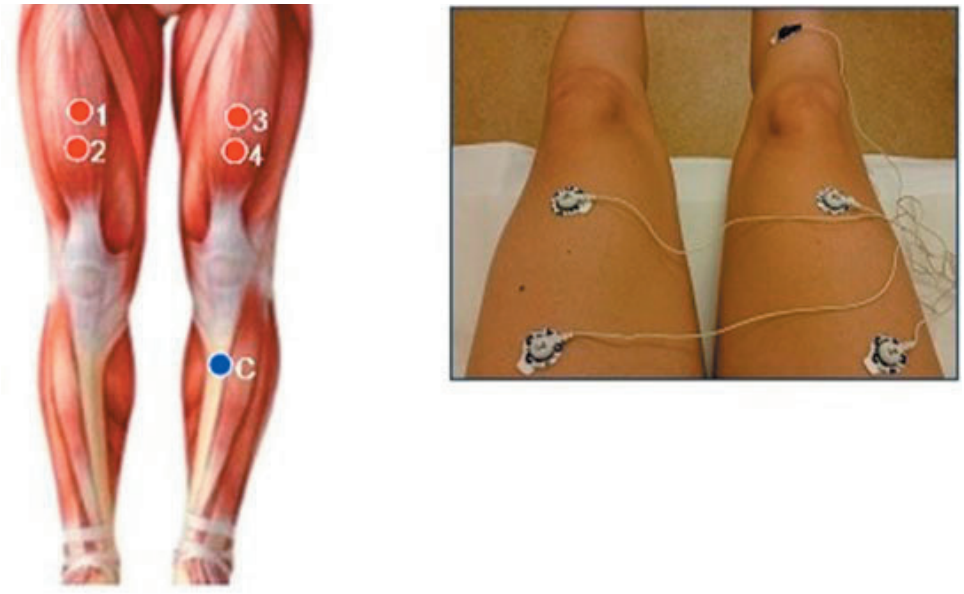
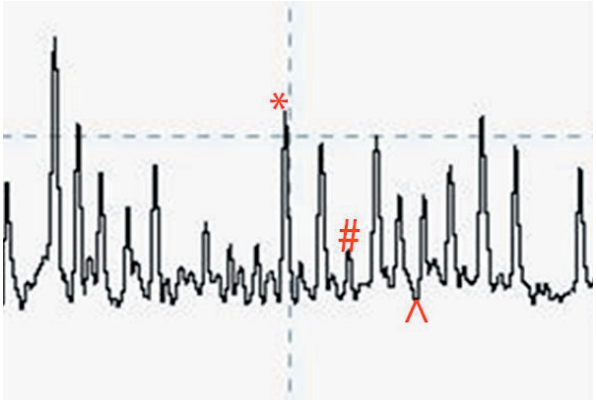


Supplementary figure 1 Position of the electrodes during bed cycling

Distal electrodes (2 and 4) were placed 5 cm above the tendon, and proximal electrodes (1 and 3) were placed 10 cm higher. The ground electrode (C) was placed on the tibia.



Supplementary figure 2 Illustration of the root mean square (RMS) from the sEMG signal

* Peak; # artifact; ^Trough

With the selected maximum of the sEMG shown as 'Peak' signals and the minimum sEMG shown as 'Trough' signals.

CHAPTER 6

Body weight-supported bedside treadmill training facilitates ambulation in ICU patients: an interventional proof of concept study

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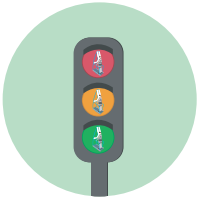

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ABSTRACT

Purpose: Early mobilisation is advocated to improve recovery of intensive care unit (ICU) survivors. However, severe weakness in combination with tubes, lines and machinery are practical barriers for the implementation of ambulation with critically ill patients.
The aim of this study was to explore the feasibility of Body Weight-Supported Treadmill Training (BWSTT) in critically ill patients in the ICU.

Methods: A custom build bedside Body Weight-Supported Treadmill was used and evaluated in medical and surgical patients in the ICU. Feasibility was evaluated according to eligibility, successful number of BWSTT, number of staff needed, adverse events, number of patients that could not have walked without BWSTT, patient satisfaction and anxiety.

Results: Twenty participants, underwent 54 sessions BWSTT. Two staff members executed the BWSTT and no adverse events occurred. Medical equipment did not have to be disconnected during all treatment sessions. In 74% of the sessions, the participants would not have been able to walk without the BWSTT. Patient satisfaction with BWSTT was high and anxiety low.

Conclusions: This proof of concept study demonstrated that BWSTT is safe, reduces staff resource, and facilitates the first time to ambulation in critically ill patients with severe muscle weakness in the ICU.

INTRODUCTION

Approximately 30–65% of the critically ill patients who are mechanically ventilated for 5–7 days develop ICU-Acquired Weakness (ICUAW).(1) ICU-AW results in difficult weaning from the ventilator and impedes recovery of muscle strength, muscular endurance and aerobic capacity and contributes to a longer hospital stay, a decrease in functioning and a reduced quality of life after ICU discharge.(2-6) Early mobilisation has become a common component of patient care in ICUs to prevent ICU-AW and to improve functional recovery.(7-9) Early mobilisation is initiated when patients are first physiologically stable, and includes progressive therapeutic activities, such as bed mobility exercises, sitting on the edge of the bed, standing, transferring to a chair, and ambulation. Recent studies have identified lack of staff and time, potential risks of airway dislodgement and dislocation of intravenous and arterial lines, and monitoring as common barriers for ambulating critically ill patients in the ICU.(10-12) To overcome the main barriers for early ambulation with critically ill patients, we developed a transportable body weight-supported treadmill (BWST) for the use at the bedside of patients in the ICU.

The premise of this proof of concept study was that BWST Training (BWSTT) is feasible and safe in the ICU, reduces staff workload and shortens first time to ambulation.

METHODS

This proof of concept study was an interventional single group design conducted in the medical and surgical closed-format ICU Intensive Care Unit (ICU) of the Academic Medical Center (AMC), University of Amsterdam, the Netherlands between February 2016 and September 2016.

Patients

All medical and surgical adult patients (≥ 18 years) admitted to the ICU and mechanically ventilated ≥ 48 h were screened for potential eligibility. Patients were screened daily for inclusion criteria until ICU discharge. Exclusion criteria were: low survival chance (imminent to death), one or more amputated lower extremities, insufficient knowledge of the Dutch language, not able to follow instructions (Short 5 item Questionnaire (S5Q) < 5) (13,14), no sitting balance, m. quadriceps muscle strength 0-1 according to the Medical Research Council (no contraction or contraction without limb movement), and contraindications for performing physical exercise according to the Evidence Statement for ICU physiotherapy (hemodynamic instability, surgical contraindications, etc. (see Supplementary information for safety criteria according to the Evidence Statement).(14,15)

Intervention

We built a custom mobile bedside treadmill with weight bearing utility in collaboration with the Instrumental Department at the AMC. The BWST enables ambulation at the bedside within the range of ventilator tubes, lines and monitoring equipment. In patients with insufficient motor control or muscle strength for independent ambulation, a gait harness can be used in combination with a weight bearing construction.

BWSTT was standardized with respect to safety checks, transfers, bodyweight support, treadmill speed and ambulation duration. Based on clinical observation, the amount of bodyweight support, duration of ambulation and treadmill speed was individually adjusted to the patient's capacity. The BWSTT stopped according to the termination criteria [see Supplementary information for termination criteria according to the Evidence Statement]. (14) BWSTT was continued until patient was discharged from the ICU. Two experienced ICU physiotherapists trained and skilled for this intervention conducted the training. During BWSTT, vital parameters were continuously observed and recorded similar to other physiotherapy and mobility interventions with critically ill patients.(14)

Fig. 1 is an illustration of the BWST.

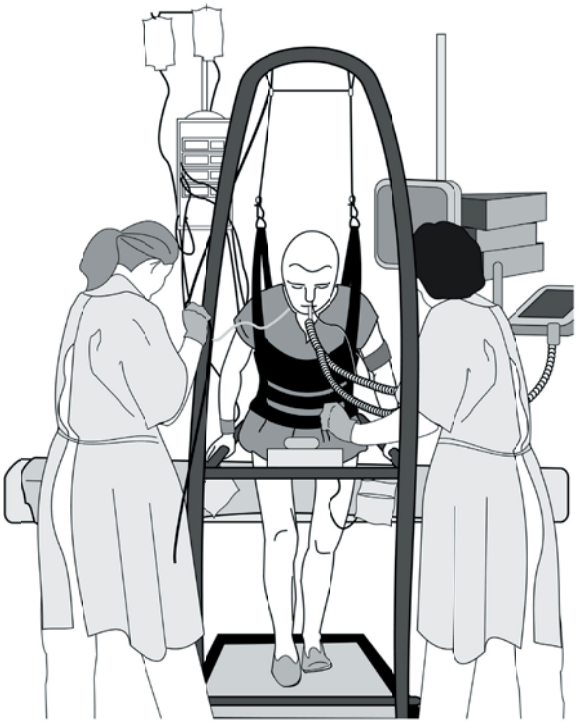

Figure 1 Schematic illustration of the body weight-supported treadmill (BWST)

Main study parameters

Main outcome measures to evaluate feasibility were: eligibility, recruitment rates, number of staff needed, adverse events (AE), successful number of BWSTT, number of patients that could not have walked without BWST, patient satisfaction (emoticons 1 = very unhappy −5 = very happy) and anxiety (numeric rating scale; 0 = no anxiety −10 = severe anxiety). Adverse events included falls, wounds, dislocation of tubes, lines or other equipment, violation of safety criteria for mobilisation during the intervention, and were classified as mild (the AE impairs the normal functional level of the subject only slightly), moderate (the AE impairs the normal functional level of the subject to a certain extent) and severe (the AE represents a clear-cut, marked impairment of the subject's normal functional level). Serious adverse events ((S)AEs) were defined as any untoward medical occurrence or effect that results in death, is life threatening (at the time of the event) requiring prolongation of hospitalization or results in persistent or significant disability or incapacity.

Patient characteristics and clinical data associated with the ICU stay were recorded. Data on functional status were expressed as muscle strength and ambulation status, using the Medical Research Council Sum Score (MRC-SS) (14,15) and the Functional Ambulation Categories (FAC).(16)

Power

Due to the explorative design of this proof of principle study, no formal sample size calculations were performed. A consecutive series of 20 evaluable ICU patients admitted for medical or surgical reasons were estimated, to explore the feasibility BWSTT.

Ethical approval

Ethical approval was obtained from the AMC local Ethics Committee (Amsterdam, the Netherlands, NL56342.018.16). Written informed consent was obtained from all participants.

Statistical analyses

Statistical analyses were performed with SPSS version 23. Descriptive Statistics were performed. All data are presented as means and standard deviations or, in case of a skewed distribution, as medians with the interquartile range (IQR) (25th – 75th percentile).

RESULTS

After 6 months 167 medical and surgical pts. (< 18 years) admitted to the ICU and mechanically ventilated for more 48 h, were screened for inclusion. Sixty-eight patients

were excluded because they were unable to walk prior to ICU admission (n= 3), overweight (n = 1), eminent to death (n = 53), had a lower extremity amputee (n = 3) or did not speak Dutch (n = 8). In 43 patients it was considered not safe to perform physical exercise according to the Evidence Statement (14), 22 patients were not able to follow instructions (S5Q < 5) and 2 patients had insufficient sitting balance (14) or m. quadriceps strength.

Of the 32 patients who satisfied the inclusion criteria, 10 were discharged from the ICU before start of the intervention and 2 did not provide informed consent.

Consequently, 20 consecutive patients who provided informed consent were included.

Fig. 2 shows the screening and inclusion process. Patient characteristics of the 20 participants at the first BWSTT are presented in Table 1.

Twenty participants underwent a total of 54 sessions BWSTT with a median (IQR) of 2 (1–3) for each participant. The median (IQR) age was 69.5 (52.8–77.5), time spent in the ICU before BWSTT was 23 (10–56) days. Median muscle strength was MRC-SS 40 (32.5–47.5) with 75% having ICU-AW (MRC-SS < 48). Sixty-five percent had a FAC score 0 (non-functional ambulator or cannot walk). All participants had ≥ 3 catheter or infusion lines (Table 1).

The walking distance per session was median (IQR) 31(3–95) steps. The median (IQR) duration of the treatment sessions, including preparation time, was 25 (20−30) minutes. The number of staff, all physical therapists, involved in preparation and treatment was 2 IQR (2-3). In 49 (91%) sessions, participants would have required the assistance of >2 persons for weight bearing support and for carrying and moving equipment (ventilator, monitor, infuses, wheelchair, etc.) in case the BWST had not been available.

No adverse events occurred and none of the medical equipment (ventilator, monitor, infuses, drains, continuous veno-venous hemofiltration (CVVH), pacemakers, etc.) had to be disconnected during the 54 sessions. Except for one, all BWSTT sessions could be executed as planned according to the protocol, without interruption or unexpected early termination. One participant started the session but was not able to walk on the BWST due to upper extremity weakness (MRC 2).

In 40 of 54 (74%) sessions, the participants would not have been able to walk without the BWST due to severe muscle weakness (FAC 0: person cannot walk, or needs help from 2 or more persons).

In 14 sessions, according to the low FAC score (1–2) and based on clinical judgement of the physiotherapist, participants would have been able to ambulate approximately 5 m without a BWST, however, with use of the BWST, the participant walked > 10 m, which is a potential increase of distance of > 100%.

Patient satisfaction was high and anxiety during BWSST low; median (IQR) satisfaction score 5 (3–5) and anxiety 0 (0–5).

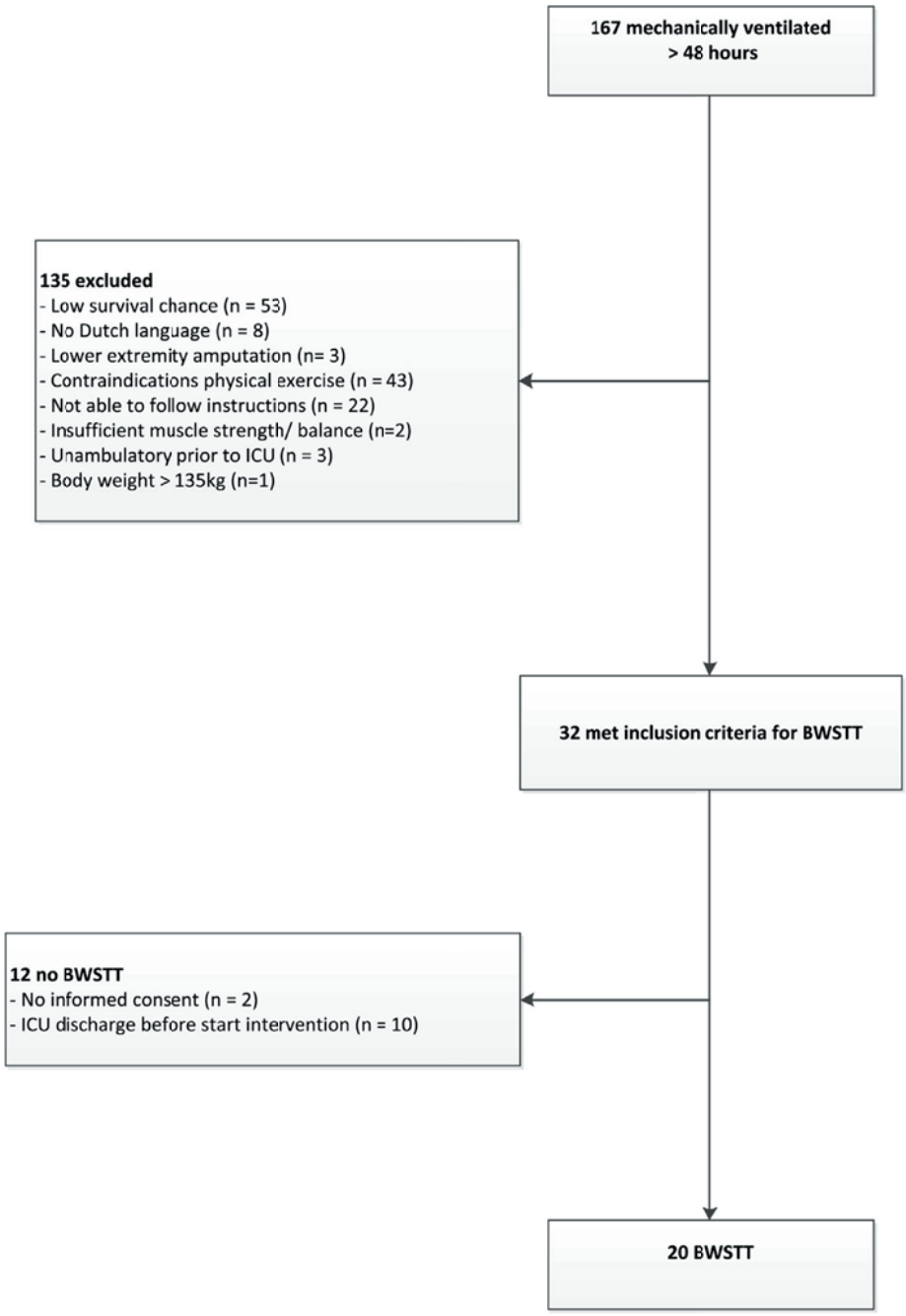

Figure 2 Flowchart of the inclusion process

Table 1 Patient characteristics at ICU admission and at first BWSTT (N= 20)

Patient characteristics	
Age, median (IQR) (years)	69.5 (52.8-77.5)
Male, n (%)	12 (60%)
BMI[a], median (IQR)	26.6 (22.2-28.1)
- BMI > 25, n (%)	12 (60%)
- BMI > 30, n (%)	2 (10%)
Reason for ICU admission	
- Medical, n (%)	9 (45%)
- Surgical elective, n (%)	7 (35%)
- Surgical emergency, n (%)	4 (20%)
Severity of illness: APACHE II[b] score, median (IQR)	18 (15-20)
Duration of mechanical ventilation, days, median (IQR)	10.0 (7.1 – 31.5)
Time in ICU to first BWSTT[c] session (days), median (IQR)	23.0 (10.0 -56.3)
[g]MRC sum-score[d], median (IQR) (range 0-60)	40 (32.5 - 47.5)
Total MRC score upper extremity median (IQR) (range 0-30)	12.0 (11.0-12.0)
Total MRC score lower extremity, median (IQR) (range 0-30)	8.5 (6.3-11.8)
ICU-AW[e] (MRC < 48), n (%)	15 (75%)
[g]FAC[f], median (IQR) (range 0-5)	0.0 (0.0 – 1.0)
- FAC 0 (unable to walk), n (%)	13 (65%)
Characteristics of ICU treatment devices	
Continuous monitoring (cardiac, ventilatory), n (%)	20 (100%)
Number of patients with mechanical ventilation, n (%)	4 (20%)
- endotracheal tube / tracheostomy, n (%)	2 (10%) / 2 (10%)
Number of patients with tracheostomy, n (%)	8 (40%)
Surgical wounds, n (%)	11 (55%)
- Sternotomy, n (%)	6 (55%)
- Abdominal, n (%)	3 (27%)
- Neck, n(%)	2 (18%)
Patients with infusion / lines, n (%)	20 (100%)
- Arterial catheter, n (%)	19 (95%)
- Intravenous catheter /Central venous catheter, n (%)	9 (45%)
- Continuous Veno-Venous Hemofiltration, n (%)	4 (20%)
a. jugularis / a. femoralis, n	1/3
- External pacemaker, n (%)	4 (20%)
Inguinal / thoracic, n	1 / 3
- Foley catheter, n (%)	20 (100%)
- Drain, n (%)	8 (40%)
Thoracic/ other, n	3 / 7
- Gastric tube	20 (100%)

[a] BMI: Body Mass Index, score > 25= obesity, score > 30 = severe obesity.
[b] APACHE II: Acute Physiology and Chronic Health Evaluation II, ranging from 0 to 71 with higher scores corresponding to more severe disease and a higher risk of death.
[c] BWSTT: Body Weight Supportive Treadmill Training.
[d] MRC-SS: Muscle strength according to Medical Research Council Sum Score, higher scores correspond to increased strength.
[e] ICU-AW: Intensive Care Unit Acquired Weakness defined as MRC-SS < 48.
[f] FAC: Functional Ambulation Categories, 6-point scale assessing ambulation status by determining how much human support the patient requires to walk. Scores range from 0: non-functional ambulator or cannot walk, to 5: independent on any surface.
[g] MRC, and FAC were measured without the BWST before the intervention.

DISCUSSION

This proof of concept study shows that the use of a bedside BWST is safe, reduces staff resource, and facilitates the first time to ambulation in critically ill patients with severe muscle weakness in the ICU, compared to ambulation without a BWST.

BWSTT has shown to be an effective modality for improving fitness, walking capacity and daily functioning in different rehabilitation populations with muscle weakness.(17-20)

As BWST is, until now, only available as fixed system in departments of physical therapy and rehabilitation medicine, this method has never been used in patients in the ICU before.

The benefits with BWSTT in other rehabilitation populations apply primarily to the decreased functional capacity and motor control by which patients could not walk without assistance. In patients with stroke, traumatic brain and spinal cord injuries it was demonstrated that BWSTT increases walking distances and gait quality.(17,18,20,21) In this study we showed that patients in the ICU who were unambulatory or required significant assistance for walking due to decreased muscle strength, were able to walk with a BWST. Impaired physical capacity is not the only reason for not ambulating patients in the ICU. In the ICU, the availability of specialized equipment and technological aids are important to maximize the safety, efficiency, and effectiveness of early mobilisation. To illustrate, in order to ambulate, a walker is necessary to provide balance and support. In addition, a wheelchair is generally pushed behind an ambulating ICU patient to permit the patient to immediately sit and rest when necessary, and to transport patients to their bed if they become physically incapable of walking due to weakness, fatigue, or medical complications. Other technological considerations include the continuation of ventilator support, the availability of a portable cardiac monitor and pulse oximeter to allow continuous vital sign monitoring during ambulation, and a wheeled pole with infusion pumps for intravenous medications that cannot be temporarily stopped during mobilisation.

Furthermore, despite the safety of early mobilisation staff must exercise significant care to ensure that catheters, tubes, and wires are secured adequately before starting ambulation and do not get tangled or removed. While ambulating, usually one or two

physical therapists will provide hands-on assistance to the patient, an ICU nurse takes care of the pole with infusion pumps, one person follows the patient with the wheelchair and one person supervises the ventilator, and monitoring of vital symptoms. The latter staffing issue has significant resource implications in the ICU and limit the number of patients who can be mobilized each day.(10,11)

Two previous studies reported on novel devices to assist with ambulating ICU patients.(22,11) The use of a wheeled walker with safety seat and tower housing portable equipment reduced the required two staff to ambulate with mechanically ventilated patients to two. Nevertheless, in order to ambulate, the ventilator, oxygen, monitor devices and infusion have to be disconnected to the consolidation on the wheeled tower. (11) One hospital designed a swimming-pool with adjustable floor for ICU patients with severe weakness. Besides the financial issues of exploiting a swimming-pool in the ICU, the duration of a hydrotherapy session is at least 60 min and requires 4 staff members for preparation and execution of the therapy.(22) We demonstrated that the use of a mobile BWST overcomes most of these practical barriers for early mobilisation in a complex environment of the ICU. Apart from all equipment, several patient characteristics were present which are generally considered as barriers for ambulation. Moreover, 13 (65%) of the patients had FAC 0, i.e. non-functional ambulation, 14 (70%) had a body mass index score (BMI) > 25, indicating obesity, and 15 (75%) had ICU-AW. By using the BWST at the bedside of the patient, it was not necessary to interrupt medical treatment, it allowed less human resource requirements, and improved the safety and effectiveness of ambulating mechanically ventilated patients.

Another potential benefit that was observed but not systematically evaluated, was that BWSTT was a strong stimulant and positive experience for the patients. Patients and their families were very satisfied with this intervention and reported that BWSTT improved their confidence in their recovery towards their previous lives and autonomy.

There are some limitations of this study. First, it was executed in one center potentially limiting the generalizability of the results. However, since the study was performed in a university hospital treating patients with an above average of complexity, we assume that the positive findings can be translated to other populations in different ICU settings.

The proportion of the screened patients that were included was rather low (12%), but as expected. The fact that nearly all included patients were able to complete BWSTT and no mild or severe adverse events occurred may indicate that we have used rather conservative safety criteria for inclusion. Moreover, due to practical reasons, we did not consider patients with neurological disorders as reason for ICU admission for inclusion in this study. Obviously, the majority of patients were enrolled shortly before ICU discharge and as a consequence the number of treatments per patient in this study was low (median 2). It could be questioned whether a (measurable) training effect could be

achieved within two sessions. However, since the aim of this study was to evaluate safety and feasibility of this novel technology in the most challenging environment, i.e. an ICU, BWSTT was stopped when the patient was discharged from the ICU. Albeit we did not measure the effects of BWSTT, we presume that continuation of BWSTT after ICU stay at the general ward would be beneficial in order to improve the effects of BWSTT in terms of muscle strength or walking capacity. According to our inclusion criteria patients had to be mechanically ventilated > 48h, conscious, meeting the safety criteria for performing active exercise according to the evidence statement, having independent sitting balance and MRC m. quadriceps strength ≥ 2 to be enrolled. This set of criteria obviously led to the enrolment of patients who had been severely ill, were treated in the ICU for median of 23 days and had median low muscle strength (MRC-SS 40) indicating ICU-AW.

As this proof of concept study showed the feasibility and safety of the use of BWST in this population who is considered to physically suffer most from consequences of critical illness and prolonged immobilisation, we assume that the population of patients that could potentially benefit from BWSTT can be increased by considering the inclusion criteria regarding ventilation, safety and extending to patients with neurological disorders.

The physiotherapists involved in this study were experienced with mobilisation of patients in the ICU and participated in the development of the novel BWST. Their involvement may have contributed to the success of BWSTT. As mobilisation of patients in the ICU and the use of the BWST require a continuous clinical judgement of potential risks, benefits as well as patient capacities, education will be necessary for a successful and wide implementation of BWSTT. Nevertheless, the protocol for this study, consisting of a precise description of inclusion criteria, safety checks, and treatment issues could be followed in all cases without any violation, indicating that this can serve as a manual for the use of BWSTT.

CONCLUSION

In conclusion, this proof of concept study demonstrates that BWSTT in critically ill patients is feasible, safe and potentially effective. Given the unique challenges of early mobilisation of critically ill patients in an ICU environment, BWSTT provides many advantages compared to manual ambulation training such as less manpower, continuation of medical treatments and earlier ambulation for patients with muscle weakness. Moreover, we found that BWSTT was a very positive experience and strong motivator for the patients improving their confidence in the recovery process. As recovery of walking ability is one of the most important milestones in the rehabilitation process and one of the factors with the most impact on social participation and professional reintegration, the results of this study may have important implications for clinical practice.

In future research we should further investigate the effects of BWSTT in critically ill patients in the ICU in terms of muscle strength, walking capacity and recovery trajectory. In addition the effects on duration of mechanical ventilation and ICU stay will be evaluated as well as the effects on costs.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Academic Medical Center (AMC) local Ethics Committee (Amsterdam, the Netherlands, NL56342.018.16). Written informed consent was obtained from all participants.

CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

J.S. and D.C.W. assisted in the design of the study, conducted the study, analyzed and interpreted the data, and J.S. drafted the manuscript.
D.A.D. assisted in the design and assisted in conducting the study.
F. N. and R.H.H.E. assisted in design of the study and reviewed the final version of the manuscript.
M.v.d.S. conceived the study, participated in its design and coordination, assisted in the data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

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APPENDIX

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.05.010

SUPPLEMENTARY INFORMATION 1

Contraindications for active exercise with patients in the ICU according to the evidence statement for ICU physical therapy (Sommers. et. al. 2013):

- Heart rate:
  Recent myocardial ischemia
  Hart frequency < 40 or > 130
- Blood pressure:
  Map < 60 or > 110 mmHg
- Pulse oxymetry:
  ≤ 90%
- Mechanical ventilation:
  FiO_2 ≥ 0.6 (60%)
  PEEP ≥ 10 cm H_2O
- Breathing frequency:
  Frequency > 40 per minute
- Dose of inotropes:
  Dopamine > 10 mcg/kg/min
  Nor/adrenaline ≥ 0.1 mcg/kg/min
- Temperature:
  ≥ 38.5 degrees Celsius
  ≤ 36 degrees Celsius
- Other:
  - Clinical observation by physical therapist: abnormal sweating, abnormal face colour, decreased level of consciousness, pain, fatigue
  - Surgical contra-indications (i.e. instable fractures, bone flap, open abdomen or thorax)
  - Presence of lines that prevent mobilisation

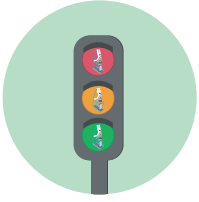
SUPPLEMENTARY INFORMATION 2

The recommendations of the evidence statement regarding stopping criteria for training are:

- Heart rate: < 40; > 130 beats/ min
- Blood pressure (MAP): < 65 mmHg; > 110 mmHg
- Respiratory frequency: > 40 breath/min
- Oxygen saturation: < 90%
- Arrhythmia
- Clinical symptoms:
  - Decreased level of awareness/consciousness
  - Sweating
  - Abnormal face color
  - Pain
  - Patient tempts to stop immediately

CHAPTER 7

General discussion



The severity of long term impairments and restrictions compromising physical functioning in patients who survive their intensive care unit (ICU) stay is to a great extent determined by the consequences of their critical illness and medical treatment in the ICU.(1-3) To limit the physical impairments in the Post-Intensive Care Syndrome (PICS), physical therapy should be initiated as soon as possible.(4-15) Several studies have illustrated a positive effect of early rehabilitation.(4-6, 8-17) Other studies did not show these beneficial effects.(18-20) The differences in study results can be explained by differences in inclusion criteria, type and load of interventions investigated, start of interventions and outcome measurements.(21)

Ideally, in order to improve physical functioning, the training load of physical therapy should be sufficient with respect to the training load principles of the Academy of Sport Sciences (Frequency, Intensity, Time and Type (FITT) parameters).(22) At the same time, exercise should be safe and physiological overload should be avoided. This is especially important in ICU patients who have a low exercise tolerance due to their critical illness that results in inflammatory responses, metabolic alterations and mitochondrial dysfunction. (23, 24)

At present, knowledge on safe and effective physical therapy for patients in the ICU is limited and no guideline is available to determine the optimal training load in this group. (4, 9, 11, 25-28)

To contribute to these gaps in knowledge and to the need for clinical practice guidelines, the studies described in the previous chapters explored:

- safety criteria to guide physical therapy in ICU patients;
- applicable and valid instruments to measure physical impairments in order to determine the goals of physical therapy;
- physiological changes and muscle activity in ICU patients during exercise;
- whether we could develop an intervention to facilitate early mobilization.

In this general discussion the main findings and methodology of the studies are reviewed, and clinical implications with recommendations for physical therapy during ICU stay as well as future research are provided.

MAIN FINDINGS

Safety criteria for physical therapy in the ICU

Patients are admitted to the ICU for monitoring, stabilizing and treatment of acute life threatening disease. Treatment often necessitates the use of mechanical ventilation, infusion lines and large intravenous cannula.(20, 29) The ICU treatment, inactivity and bedrest result in a decrease of muscle strength and a reduction in the cardiovascular and respiratory condition.(30, 31) Typically, ICU patients are attached to several supportive devices (e.g.

mechanical ventilation, continuous renal replacement therapy), are hemodynamically instable and respiratory insufficient, and have low exercise tolerance. Therefore, physical therapy can be difficult to execute and may have health risks. Maintaining the safety of ICU patients during physical therapy is important. Adverse events such as accidental removal of endotracheal tube and central lines, hypotension, hypoxia and falls should be avoided. (5, 18) To prevent these accidents, identification of patients with high risk of adverse events is required. As no guidelines or recommendations on these topics were available, we developed safety criteria using the 'Dutch Evidence Based Guideline Development Platform' (EBRO method) **(chapter 2)**.(32, 33) These criteria consist of cut off values of respiratory and hemodynamic parameters and level of consciousness to guide clinical decision making regarding when it is safe to start, or stop physical therapy treatment in ICU patients. They can easily be applied in daily clinical care at the bedside. After publication of our recommendations, two other papers on this topic, with similar conclusions, were published. The similarity between the recommendations corroborates our advice.(34, 35) Notably, all studies on this topic so far excluded ICU patients with neurological disorders. Future research should investigate whether the existing criteria also apply for ICU patients with neurological disorders or that the recommendations have to be adapted.

Measurement tools in the ICU for guidance of physical therapy

For patient tailored physical therapy treatment goals should be determined in line with the classification system International Classification of Functioning, disability and health (ICF) which distinguishes different domains to classify the functional consequences of a disorder.(36-38) The domain "body functions and structures" can be used to assess the physical impairments in body functions, activities and the ability to tolerate exercise of ICU patients. With this information and clinical reasoning, goals can be set for the individual patient and a tailored treatment strategy can be developed and evaluated. In our recommendation **(chapter 2)** we advised the use of specific measurement instruments which can be used in the ICU setting for the assessment of the ICF-domains "body functions and structures" and "activities". Within the literature, there is consensus on how to measure physical impairments within the ICF-domain "body functions and structures". Muscle strength can be assessed with the Medical research Council (MRC) sum score or the hand held dynamometer.(39, 40) For range of motion the goniometer can be used in ICU patients. (41) Yet, there are no recommendations for the use of instruments for measuring "activities" in this population.(31, 42-45)

In a majority of patients with PICS, mobility related activities remain limited for months up to years after ICU stay.(46) With respect to goal setting and the evaluation of treatment, we consider mobility, which is part of the "activities" domain as an important clinical outcome measure.

The "de Morton Mobility Index" (DEMMI) was originally developed to measure mobility in hospitalized elderly patients.(42-44) In **chapter 3** we investigated the psychometric properties of the DEMMI for use in the ICU.(45) We found this measurement tool to be feasible, reliable and valid for assessment of bed mobility, transfers and walking in ICU patients. It can detect a low level of mobility and is sensitive for measuring small improvements. Based on the psychometric properties in various populations outside the ICU, the DEMMI was also proposed for the measurement of mobility after ICU discharge at the regular ward and after return to the community.(31, 42-44, 47) Therefore, we recommend the DEMMI to be used as a tool for follow-up of ICU patients over the entire hospital admission and rehabilitation process.(48) Other validated measurement tools, such as the Barthel index and the Physical Function ICU Test (PFIT) are being used in several ICU's outside the Netherlands.(49-51) These instruments have disadvantages of being multidimensional or too difficult for use in daily practice for ICU patients. Furthermore, the baseline abilities measured in these scales are usually more complex than the possibilities of the recovering ICU patient, leading to a floor effect of the scale.(45, 50-54) The Functional status score for the intensive care (FSS-ICU) and the Chelsea critical care physiotherapy assessment tool (CPAx) have also been validated for ICU patients.(54, 55) Whether they are also applicable for the part of the hospital admission after the ICU is currently unknown.(56)

Physiological changes and muscle activity in ICU patients during exercise

Despite the fact that we could provide recommendations to determine the type of physical therapy interventions in **chapter 2**, guidelines on the FITT parameters for physical training in an ICU are not available. Furthermore, it is unknown whether the training principles that are used in healthy persons or other patient populations can be used for ICU patients. It is currently not understood how ICU patients physiologically respond to exercise. This knowledge gap leads to suboptimal treatment strategies with risk of under-, or over training, potentially harming patients. Therefore, we explored whether we could measure physiological changes during incremental exercise testing as well as muscle activity using surface electromyography EMG (sEMG) during bed cycling **(chapter 4 and 5)**.

In **chapter 4** we observed an increased heart and breathing frequency in rest compared to a healthy population.(57) No changes in cardiorespiratory parameters during passive cycling were observed, whereas during active cycling with incremental resistance a limited, but significant, increase in these parameters was measured. It is questionable whether these changes imply that the applied exercise load was sufficient to induce physiological responses to improve the cardiorespiratory condition. We propose that ICU patients do not reach cardiorespiratory endpoints during incremental testing. Moreover, we observed that these patients stopped cycling early due to muscle weakness

and generalized fatigue (based on the Borg RPE scale) **(chapter 4)**. Normative values for cardiorespiratory parameters in response to exercise are based on healthy subjects, and are therefore likely not applicable to ICU patients. It has been described that as a consequence of the metabolic response to stress, the cardiac output and resting heartrate are increased.(28, 58, 59) Also Preiser and colleagues found that different mechanisms increase the distribution of energy sources to vital tissues and stimulate the sympathetic nervous system and pituitary hormones.(28) These mechanisms might partly explain our findings of an increase in heart and breathing frequency in rest.

Muscle activity during cycling can be measured by sEMG **(chapter 5)**. We found an increase in $sEMG_{max}$ in the ICU and control groups during incremental resistance. The trough values ($sEMG_{min}$) showed no change in the patient group but an increase in the control group. These results can currently not be explained easily, therefore larger populations and different study setting are needed. Interestingly, we already observed muscle activity during passive cycling, both in ICU patients and healthy controls. These results support findings of other studies, which demonstrated positive effects of passive cycling on muscle status. They concluded that passive cycling may reduce the loss of muscle mass and limit the inflammatory process.(4, 10, 60, 61)

Development of an intervention to facilitate mobilization

In **chapter 6** we showed that the equipment we specifically developed to enable controlled ambulation "the body weight supported treadmill (BWST)", is feasible to be used in the ICU with continuous monitoring of vital signs and medical treatment. The BWST can also easily and safely be used with the support of only two persons. This is a major step forward in comparison with current practice which implies the disconnection of many ICU devices, requires that the patient has sufficient muscle strength to maintain an upright position, and the assistance of at least four people .

In the BWST, the patient is supported with a safety harness, enabling weak patients to start with walking training very early in their recovery process.

Offering a safe and controlled environment, the BWST allows the investigation of cardiorespiratory and muscle responses during exercise. This device offers an excellent opportunity for future research towards early, effective physical training in ICU patients.

METHODOLOGICAL CONSIDERATIONS

Study population

Dutch data sets show that most ICU patients are admitted for only two days.(62) This population consists partly of uncomplicated postsurgical patients admitted to an ICU for a short observation period. These patients are not expected to develop muscular weakness

or PICS. For the studies in this thesis we were interested in patients with a long duration of ICU stay and therefore a high risk of developing severe weakness and PICS. Therefore, we included only patients who were mechanically ventilated in the ICU for more than 48 hours.(1-3, 63) Consequently, our study populations do not represent the general Dutch ICU population.

For the pilot studies described in **chapter 5 and 6** we only included patients in the ICU of the Amsterdam University Medical Center, location AMC. It can be expected that the patient population in this high referral center is different from patients in other ICUs. Patients in the ICU of the Amsterdam University Medical Center, location AMC might be more severely ill with more severe physical impairments and restrictions, potentially limiting the generalizability of our results to other ICU settings.

The study populations in our studies were treated as part of usual care by the physical therapists to prevent physical impairments and improve physical functioning. By using the safety criteria as described in **chapter 2** as inclusion criteria, we selected those patients for whom it was safe to perform the physical therapy interventions as described in the studies of **chapter 4, 5 and 6**. In order to test new technologies and to avoid the possible risks in large groups of patients, we deliberately used pilot studies as first step for investigating "innovative" methods such as the bed cycling exercise test and the intervention BWST training. Furthermore, we excluded neurological patients admitted to the ICU because of e.g. acute brain injury. This patient group is often excluded from studies investigating physical therapy on the ICU (64), mainly because the outcome is not only determined by the critical illness and ICU treatment, but also by the brain injury itself.

We realize that the selection criteria that we applied in our studies may limit the generalizability of our results to the patient groups that we excluded. Therefore, our studies need to be repeated in other ICUs and other populations at risk for PICS.

Measurements

In **chapter 4** we investigated the response to incremental exercise during cycling based on measurements of oxygen uptake and carbon dioxide expiration. In patients on mechanical ventilation this was possible, whereas in detubated patients who still needed oxygen, a canopy hood had to be used. The oxygen supplementation in combination with the canopy hood yielded invalid results leading to the exclusion of a large group of patients at risk of developing PICS.(65) An adapted measurement method especially for this group of patients would enable the measurement in these patients.

A limitation of the bed-based cycle that was used in **chapter 4 and 5**, was that it did not provide information about the precise workload in Watts. The bed-cycle lacked the option that the workload could be set at a fixed wattage per minute. The software chose its own increase, based on the standardized steps algorithm of the cycle. The availability

of this information would have enabled analyses on the cardiorespiratory condition given the resistance at that moment. New cycles allowing such analyses are available but they are not suitable for ICU patients yet, as even the lowest possible resistance level is too high for these severely ill patients. If these cycles would be adapted and would become available for ICU use, research could investigate the exact dose response relationship, i.e. cardiorespiratory responses to a specified incremental workload. This knowledge is required for more effective physical therapy in ICU patients to preserve and restore physical condition and faster recovery of physical functioning.

CLINICAL IMPLICATIONS WITH RECOMMENDATIONS FOR PHYSICAL THERAPY

The next step after writing guidelines and recommendations is implementation and valorization. From the literature it is known that for successful implementation, both knowledge as well as attitude and culture have to be addressed in educational programs. (6, 66) Shortly after publication of the evidence statement **(chapter 2)** education about the safety criteria and the Core Outcome Set (COS) of measurements was initiated. The post graduate course 'Physical therapy in the intensive care' by the Dutch Institute of Allied Health Care was established and attended by a large number of physical therapists. In addition, a manual accompanying the evidence statement was published in Dutch to facilitate the implementation into daily practice.(67) The impact of these implementation and valorization activities was investigated (Evaluation Dutch Association of Hospital Physical Therapy; Nederlandse Vereniging van Ziekenhuis fysiotherapie; NVZF, 2015 [not published]). A survey was send to departments of physical therapy in 40 Dutch hospitals and filled out by ICU physical therapists. The results showed that the safety criteria were implemented in 80% of the hospitals. The COS was used in 63% of the ICUs, whereas the Medical Research Council (MRC) sum score and the DEMMI were not used on a regular basis. The causes for this limited implementation of the COS are currently unknown. Implementation of the safety criteria may be easier in daily practice than more complex clinimetric tools. From the feedback on the post graduate course in the Dutch Institute of Allied Health Care program we concluded that the awareness for the need of, and interest in physical therapy on the ICU has grown and that the recommendations from the evidence statement **(chapter 2)** seem to contribute to the implementation.

Despite the successful implementation so far, awareness of the importance of early physical therapy, and the need for activities to facilitate the use of clinimetrics and early physical therapy in daily practice, are still indicated.

The COS with instruments for physical therapy in the ICU as proposed in the evidence statement **(chapter 2)** could form the basis for the further implementation of clinimetrics and for further quality improvement within the Netherlands. For this purpose, education on the daily use of the measurement tools in an ICU should be established. Furthermore, the COS should be collected in a national registry in Dutch hospitals. Such a registry should ideally also record detailed information about physical therapy intervention as applied. With this information, physical therapy decision making and clinical practice can be compared between different ICUs for quality purposes. In addition, large datasets enable detailed analyses for risk stratification and effectiveness of physical therapy in specific patients groups.(21)

A next step towards improving physical therapy on the ICU would be the earlier start of passive physical therapy. Based on the results of Kayambu et al, Burtin et al, Griffiths et al, and Winkelman et al who described the benefits of passive cycling and our results from **chapter 5**, this seems to be beneficial.(4, 10, 60, 61) This implies that physical therapy with passive bed cycling exercise might be initiated earlier than currently indicated by the safety criteria **(chapter 2)**.

As soon as possible, the switch should be made from passive to active exercise and functional physical therapy interventions for ICU patients. An adequate training stimulus is required to achieve physiological training responses with respect to muscle strength, cardiorespiratory condition and physical activities, however the risk of overloading ICU patients is high. Although valid measurements are available for exercise capacity testing in healthy people, such as the Cardiopulmonary Exercise Test (CPET), these tests should be adjusted and validated for ICU patients in different phases of their recovery. We performed a pilot study with an incremental exercise test and observed, despite of not reaching the cardiorespiratory endpoints, a remarkable discrepancy between the small changes in physiological response and the relatively high perceived exertion as measured with the Borg RPE scale. The high Borg RPE score might have been influenced, by additional factors, such as pain or anxiety. Furthermore, the Borg RPE score is likely to be affected by the critical illness in general. This alters metabolism, increases inflammation and has many other effects. These aspects were not evaluated in our studies **(chapter 4 and 5)**.

Considering the high risk of overloading in these vulnerable patients, preferably, additional to vital parameters, information on cardiorespiratory effort, muscle activity and perceived exertion should be available during physical therapy. This will allow to further study the training dose-response relationship in critical illness. Since we have no validated training principles in ICU patients, we recommend to determine the exercise intensity based on the safety and stop criteria, the Borg RPE scale and the number of repetitions that was achieved earlier. The same parameters can also be used for the evaluation of physical therapy interventions.

Given the limited exercise tolerance, repeated short periods of closely monitored exercise seems to be the best option.(68) In such a program, a combination of strength training and cardiorespiratory training as well as improvement of activities of daily living (ADL) should be included, enabling activation of the different types of energy systems.(68, 69) In addition to the different training sessions, sufficient recovery and rest should be taken into account.(69) For functional training, independent walking is of great importance. In the ICU, the availability of specialized equipment and technological aids are important to maximize effectiveness and efficiency of early mobilization. Therefore, ambulation with the BWST is promising but should be investigated with respect to effectiveness first.

To establish an optimal daily program with repeated physical therapy sessions, both ICU nurses and family members should be involved. Active involvement of family members in hospital care has been shown to improve the quality of patient care.(70, 71) During the training program, adequate monitoring is crucial to prevent over- and under stimulation. This patient centered approach requires tailored education for, and collaboration between the ICU professionals and family members.(6, 72, 73)

FUTURE RESEARCH

To develop ICU physical therapy for the next decennium several steps have to be made. First, the recommendations with respect to the safety criteria **(chapter 2)** should be validated. The criteria were established with experts and have not systematically been evaluated in clinical practice. Furthermore, safety criteria for ICU patients admitted with acute brain injury should be developed. This is a large group of patients who might benefit substantially from early physical therapy.

Second, from top sport settings, we can use the available knowledge to optimally adjust training to induce physiological responses, while avoiding overload and allowing sufficient recovery periods. In top sports, monitoring tools and systematic measurements are being used to continuously adjust individual training programs. This knowledge and these methods should be adapted and validated for use in the ICU setting. Normative values of these measures for the ICU population should be developed. Based on this, better tailored training schedules can be determined and evaluated.

As soon as the life-threatening phase of the disease has passed, these measures should be used to determine the initial training capacity and parameters. As the patient recovers, measurements should be repeated on a regular basis by which the training program can be individually tailored and adjusted to align with the recovery process.

Based on our experience, such an ICU monitoring tool should also include information on the load of the bed side ergometer that is used on the ICU. Based on the combination of cardiorespiratory parameters, muscle activity measurements, cycling parameters and the Borg RPE scale, tailored physical therapy interventions can be developed and evaluated.

We observed that many ICU patients were too weak for active cycling on the ergometer in the lowest possible load. Therefore a bed side ergometer with a "start-engine" facilitating the first revolutions, should be useful.(74)

Third, registration of the COS for ICU physical therapy in a national registry would enable to develop a large database with physical outcome measures. In future research we will be able to analyze course of recovery and risk factors that determine this course.(21)

Finally, functional training is very important as the ultimate goal for the patients is ADL independence, in which independent walking is a crucial step. The BWST which has recently been developed **(chapter 6)** can be an important next step. This potentially enables early walking. Its effectiveness is currently investigated (STEPS study: NTR: 6943) in a multicenter randomized controlled trial. This novel device will become commercially available in the near future and can, when effective, be implemented in the daily ICU care. The application of the BWST in other patients groups, such as patients with acute brain injury, or in other phases of the hospital admission has also great potential, and needs to be investigated.

CONCLUSIONS

Physical therapy contributes significantly to the recovery of ICU patients who survive and are at increased risk of developing PICS. It might prevent and reduce physical impairments and limitations in physical functioning leading to serious long term disability. The studies in the present thesis contribute to the knowledge on safety, measuring physical functioning, the physiological response to exercise and the application of this knowledge into daily clinical practice of physical therapy on the ICU. Further research towards accurate assessment of physiological responses to exercise and trainability in ICU patients is needed. Based on further evidence, patient-tailored physical therapy interventions can be developed adapted to the changing situation during the acute phase and recovery.

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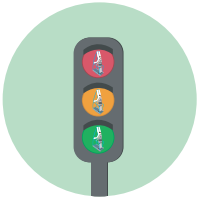
Summary

Physical therapy for patients in the Intensive Care Unit
Towards safe and purposeful physical therapy practice for critically ill patients



Along with improving medical treatment, the survival rate of patients admitted to an Intensive Care Unit (ICU) rises, leading to an increasing number of patients with long term psychological and physical impairments. These impairments are described since 2012 as "Post-Intensive Care Syndrome"(PICS).

Many ICU survivors develop muscle weakness and reduced exercise tolerance. Early rehabilitation for ICU patients has been advocated to prevent physical deterioration. However, knowledge on safe and effective physical therapy in ICU patients is lacking. In this thesis aspects of physical therapy on the ICU were investigated.

In **chapter 1**, the impact of critical illness on physical functioning, the role of physical therapy in the ICU and the rationale underlying the aims of this thesis are introduced.

Chapter 2 describes the development of evidence based recommendations for physical therapy for patients in the ICU. To compose these recommendations, the "Dutch Evidence Based Guideline Development Platform" (EBRO method), a Delphi method combining the available evidence with expert opinion, was used. These evidence-based clinical recommendations for ICU physical therapy consist of 1) indications and contra-indications for early mobilization and physical exercise: "the safety criteria", 2) a core set of instruments to assess physical functioning and activities within the International Classification of Functioning (ICF) framework, and 3) recommendations for effective evidence-based interventions.

Several knowledge gaps were identified during the development of the recommendations. The measurement instrument that was recommended to evaluate mobility in patients in the ICU, the "de Morton Mobility Index (DEMMI)", had not been validated for ICU patients. Also, recommendations for the optimal training load was not available. Moreover, knowledge regarding the physical response to exercise in ICU patients was found to be lacking. In the subsequent studies, we explored these topics aiming to resolve these knowledge gaps.

In **Chapter 3** we investigated the feasibility, reliability and validity of the DEMMI for measuring functional status according to the ICF activity domain. This was studied in 115 ICU patients. The DEMMI was assessed repeatedly during and after the ICU stay and the validity was evaluated by correlating with other measurement instruments such as the Barthel index, the Katz Index of Independence in Activities of Daily Living (Katz-ADL) and manual muscle testing. The feasibility was evaluated by examining the percentage of patients in which the DEMMI could be assessed, the floor and ceiling effects, and the number of adverse events. The DEMMI was found to be a reliable, valid and feasible measurement tool in the ICU population. Because of the absence of floor and ceiling effects during and after ICU stay, the DEMMI was recommend to measure functional status throughout the rehabilitation process.

The next two chapters contain pilot studies that explored the physiological responses to exercise in ICU patients. In **chapter 4,** we investigated the feasibility and safety of exercise testing and their physiological response to incremental exercise. A bed-based cycle ergometer with a standardized 1-minute incremental resistance was used. Depending on muscle strength, a passive or an active incremental exercise test was performed in 37 ICU patients. The feasibility and safety were evaluated by completion of the test and occurrence of adverse events. Nearly all (89%) patients completed the test and one moderately severe adverse event occurred. During active cycling a limited increase in respiratory frequency, oxygen uptake, carbon dioxide output and lactate, was found. It is questionable whether these changes imply that the applied exercise load was sufficient to induce physiological responses to improve the cardiorespiratory condition. The cardiorespiratory endpoints which are normally used in healthy persons, were not reached in the ICU patients. Reasons for not completing the test were generalized fatigue and reduced muscle strength. During passive cycling, no cardiorespiratory changes were observed. We concluded that incremental exercise testing on a bed-based cycle ergometer is feasible and safe in ICU patients. Furthermore a measurable physiological response was found during active cycling. However, solid conclusions regarding the clinical value of the changes in physiological parameters observed cannot be made. Normative values for cardiorespiratory parameters in response to exercise are based on healthy subjects, and are therefore not applicable to ICU patients. Future research is indicated for the clinical interpretation and validation of physiological changes during exercise in ICU patients.

In **chapter 5** surface electromyography (sEMG) was used to assess the changes in electrical activity of the m. quadriceps during bed cycling. In the study, nine ICU patients and six healthy controls were measured. A standardized 1-minute incremental resistance protocol with a maximum duration of 12 minutes was used. The patients cycled for a shorter period than the healthy controls (median cycle time 5.3 minutes versus 12.0 minutes). The patients stopped because of muscle fatigue in the legs. By increasing cycling resistance, a notable increase in muscle activity as assessed with sEMG was found in both groups. Also, during passive cycling already limited muscle activity was detected. These results support the observations in the literature that passive cycling may moderate the loss of muscle mass. This study showed that sEMG is feasible and can detect muscle activity during bed cycling in ICU patients. Further research should explore the response to exercise and muscle fatigue, combining measurements of cardiorespiratory parameters, muscle activity measurements and workload during an incremental exercise test on a bed side cycle ergometer.

In **chapter 6**, the feasibility of early ambulatory training with a body weight supported treadmill (BWST) was described. Ambulation with ICU patients is difficult due to reduced muscle strength and cardiorespiratory deconditioning. Other specific barriers for

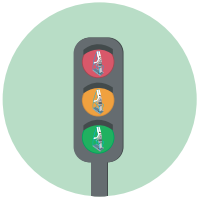
ambulation in the ICU are infusion lines, tubes and monitor equipment that are attached to the patient. Fifty-four sessions of BWST training were performed in twenty ICU patients. The feasibility was determined by the number of successful BWST training sessions, the number of patients that could not have walked without BWST training, required number of staff, duration time of the intervention, adverse events, patient rated satisfaction and anxiety of the patient. The experimental set-up required that two physical therapists were needed to perform BWST training, the time of the total intervention was 25 minutes, and except for one, all patients could perform the BWST training. No adverse events occurred. In 74% of the sessions, the patients could not have been able to walk without the BWST. The patient satisfaction was high and anxiety low. This study showed that training with the BWST is safe, reduces staff involvement and facilitates the first time to walk with patients in the ICU.

The general discussion **(chapter 7)** summarizes the main findings and limitations of this thesis. Also, recommendations for patient tailored physical therapy in the ICU and future research are provided.

This thesis contributes to the knowledge of safety, measuring physical functioning, the physiological response to exercise, and the application of this knowledge into daily clinical practice of physical therapy in the ICU.

Samenvatting

Fysiotherapie voor patiënten op de Intensive Care
Op weg naar een veilige en doelgerichte fysiotherapeutische behandeling voor de kritiek zieke patiënten



Door verbeteringen in de medische zorg is de overlevingskans van patiënten die worden opgenomen op een intensive care (IC) gestegen. Dit leidt tot een toenemend aantal patiënten met langdurige psychische- en fysieke beperkingen. Deze beperkingen, worden sinds 2012 beschreven als het "Post-Intensive Care Syndroom" (PICS).

Veel IC-overlevenden ontwikkelen ernstige spierzwakte en verminderde inspanningstolerantie. Vroegtijdige revalidatie wordt aanbevolen om de fysieke achteruitgang te beperken. Er is echter onvoldoende kennis over hoe fysiotherapie veilig en effectief kan worden aangeboden aan patiënten op de IC. In dit proefschrift zijn verschillende aspecten van fysiotherapie op de IC onderzocht.

In **hoofdstuk 1** wordt de impact van de kritieke ziekte op het fysiek functioneren, de rol van de fysiotherapie op de IC en de onderbouwing van de doelstellingen van dit proefschrift geïntroduceerd.

Hoofdstuk 2 beschrijft de ontwikkeling van evidence-based aanbevelingen voor fysiotherapie op de IC. Voor het opstellen van deze aanbevelingen, werd gebruik gemaakt van de "Evidence Based Richtlijn ontwikkeling" (EBRO-methode), een Delphi-methode die het beschikbare bewijs combineert met de mening van de experts in het veld. Deze evidence-based aanbevelingen voor fysiotherapie op de IC bestaan uit 1) indicaties en contra-indicaties voor het mobiliseren en activeren; "De veiligheidscriteria", 2) een set van meetinstrumenten om het fysieke functioneren op het gebied van "functies en anatomische eigenschappen" en "activiteiten" binnen de domeinen van het International Classification of Functioning, Disability and Health (ICF) te kunnen beoordelen, en 3) aanbevelingen voor effectieve interventies.

Tijdens de ontwikkeling van de aanbevelingen werden verschillende lacunes in de kennis geïdentificeerd. Het meetinstrument dat werd aanbevolen om de mobiliteit van patiënten op de IC te evalueren, de "de Morton Mobility Index (DEMMI)", bleek niet gevalideerd voor IC-patiënten. Daarnaast waren er geen aanbevelingen voor de optimale trainingsbelasting en ontbrak kennis over de fysiologische reactie op inspanning bij IC-patiënten. In de daaropvolgende onderzoeken hebben we kennis ontwikkeld die gericht was op deze lacunes.

In **hoofdstuk 3** hebben we de uitvoerbaarheid, betrouwbaarheid en validiteit van de DEMMI onderzocht voor het meten van de functionele status binnen het ICF domein "activiteiten". Dit werd onderzocht bij 115 IC-patiënten. De DEMMI werd herhaaldelijk gemeten gedurende en na de IC-opname. De validiteit van de DEMMI werd beoordeeld door correlatie met verschillende meetinstrumenten, waaronder: de Barthel-index, de Katz-ADL schaal en de manuele spierkrachtmetingen. De uitvoerbaarheid werd geëvalueerd door het aantal patiënten waarbij de DEMMI kon worden beoordeeld, de vloer- en plafondeffecten van de meetinstrumenten en het aantal ongewenste gebeurtenissen tijdens het afnemen van de DEMMI. De DEMMI bleek een uitvoerbaar, betrouwbaar en

valide meetinstrument te zijn voor gebruik bij IC-patiënten. Vanwege de afwezigheid van de vloer- en plafondeffecten tijdens en na het IC- verblijf, werd aangeraden om de DEMMI gedurende het gehele revalidatie proces, voor het meten van de functionele status, te gebruiken.

De volgende twee hoofdstukken bevatten pilotstudies die de fysiologische reactie op inspanning bij IC-patiënten onderzoeken. In **hoofdstuk 4** onderzochten we de uitvoerbaarheid en veiligheid van een inspanningstest met de daarbij behorende fysiologische reacties bij oplopende inspanning. Voor de inspanningstest werd een bed-fietsergometer gebruikt, waarbij de weerstand na elke minuut op een gestandaardiseerde wijze werd verhoogd. Afhankelijk van de spierkracht, werd een passieve of actieve inspanningstest uitgevoerd bij 37 IC-patiënten. De uitvoerbaarheid en veiligheid werden geëvalueerd aan de hand van het aantal patiënten dat de test kon voltooien en het aantal ongewenste gebeurtenissen. Bijna alle (89%) patiënten voltooiden de test. Eén matig ernstig ongewenste gebeurtenis trad op. Tijdens het actief fietsen werd een lichte stijging van de ademfrequentie, zuurstofopname, koolstofdioxide en lactaat waargenomen. Het is onbekend of de belasting en de hiermee gepaard gaande fysiologische veranderingen voldoende was om de cardiorespiratoire conditie te kunnen verbeteren. De cardiorespiratoire eindpunten die normaal bij gezonde personen worden gebruikt, werden niet bereikt bij de IC-patiënten. Redenen waarom de patiënten de test niet konden afmaken waren, algehele vermoeidheid en verminderde spierkracht. Tijdens passief fietsen werden geen cardiorespiratoire veranderingen waargenomen. We concludeerden dat inspanningstesten op een bed-fietsergometer bij IC-patiënten veilig kunnen worden toegepast en dat er vervolg onderzoek moet worden uitgevoerd naar de klinische betekenis van de fysiologische veranderingen.

In **hoofdstuk 5** werden oppervlakte elektromyografie (EMG) meting gebruikt om de veranderingen in elektrische activiteit van de m. quadriceps tijdens fietsen in bed te beoordelen. In deze studie werden negen IC-patiënten en zes gezonde proefpersonen gemeten. Er werd gefietst met een gestandaardiseerd oplopend weerstandsprotocol met een maximale duur van 12 minuten. De patiënten fietsten een kortere periode dan de gezonde proefpersonen (mediane fiets tijd van 5,3 minuten versus 12,0 minuten). De patiënten stopten vanwege spiervermoeidheid in de benen. Tijdens het fietsen met oplopende weerstand werd in beide groepen een meetbare spieractiviteit, middels oppervlakte EMG waargenomen. Tijdens het passief fietsen werd een geringe spieractiviteit gedetecteerd. Deze resultaten komen overeen met bevindingen vanuit de literatuur, dat passief fietsen het verlies van spiermassa kan beïnvloeden en wellicht ook kan beperken. Deze studie toonde aan dat oppervlakte EMG meting uitvoerbaar is en dat spieractiviteit bij IC-patiënten tijdens fietsen in bed gemeten kan worden. Verder onderzoek naar de reactie op inspanning en spiervermoeidheid is noodzakelijk. Hiervoor

dient een onderzoeksopstelling met verschillende meetinstrumenten (cardiorespiratoire parameters en spieractiviteit) tijdens een inspanningstest met oplopende weerstand (bedfiets-ergometer) gebruikt te worden.

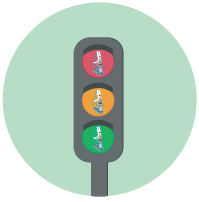
In **hoofdstuk 6** werd de haalbaarheid van vroege looptraining met een loopband met gewichtsondersteuning beschreven. Lopen met IC-patiënten is moeilijk vanwege de verminderde spierkracht en cardiorespiratoire deconditionering. Andere specifieke belemmeringen voor het lopen op de IC zijn infuuslijnen, een monitor en beademingsapparatuur waaraan de patiënt is aangesloten en de aanwezigheid van voldoende personeel (gemiddeld vier personen) om voldoende ondersteuning voor patiënt en apparatuur te kunnen bieden. Vierenvijftig sessies met gewicht ondersteunende loopbandtrainingen werden uitgevoerd bij twintig IC-patiënten. De haalbaarheid werd bepaald op basis van het aantal succesvolle loopbandtrainingen, het aantal patiënten dat zonder loopbandtraining niet had kunnen lopen, het vereiste aantal personeelsleden, de duur van de interventie, het aantal ongewenste gebeurtenissen de mate van angst en de mate van tevredenheid van de patiënten. Voor het uitvoeren van de loopbandtraining met gewichtsondersteuning waren twee fysiotherapeuten nodig. De behandelduur van een loopbandtraining bedroeg 25 minuten. Alle patiënten, behalve één, konden de training uitvoeren. Er waren geen ongewenste gebeurtenissen. In 74% van de sessies hadden de patiënten niet zonder de loopband kunnen lopen. De tevredenheid van de patiënten was hoog en men was niet angstig. Uit deze studie bleek dat trainen met de loopband veilig is, dat er minder personeel aanwezig hoeft te zijn en dat IC patiënten met spierzwakte eerder kunnen beginnen met loopbandtraining dan met reguliere looptraining.

De algemene discussie **(hoofdstuk 7)** vat de belangrijkste bevindingen en beperkingen van dit proefschrift samen. Ook worden er aanbevelingen gegeven voor aangepaste fysiotherapie op de IC en voor toekomstig onderzoek.

Dit proefschrift draagt bij aan de kennis over fysiotherapie bij IC patiënten met betrekking tot de veiligheid, het meten van het fysiek functioneren, de fysiologische respons op inspanning en de toepassing van deze kennis in de dagelijkse klinische praktijk.

Curriculum vitae

Portfolio



Juultje Sommers was born on March 26th 1969 in Amsterdam, the Netherlands. In 1989 she graduated from secondary school at the Spinoza Lyceum in Amsterdam. Between 1990 and 1994 she studied physical therapy at the Amsterdam University of Applied Science. In 1994 she worked at different private physical therapy office's. Since 1995 she works as a clinical physical therapist. Where she started at the department of Rehabilitation Medicine of the Academic Medical Center in Amsterdam. In this hospital she became interested in the treatment of patients in the Intensive Care. Because here drive of quality improvement projects, she followed a Master study and received her Master degree of Physiotherapy of the University of Leuven, Belgium. In 2001 she became quality employee and clinical physical therapist in the Onze Lieve Vrouwe Gasthuis in Amsterdam. In these years she became an expert in clinical improvement and implementation projects. In 2011 she started with an clinical improvement project, "early mobilization and activation" in the Intensive Care of the Academic Medical Center In Amsterdam. Which was followed by her PhD research "Physical therapy for patients in the Intensive Care Unit", this was supervised by prof. dr. Frans Nollet, prof. dr. Raoul Engelbert, dr. Janneke Horn and dr. Marike van der Schaaf at the department of Rehabilitation Medicine in the Amsterdam UMC, location AMC in Amsterdam.

Besides her work as a physical therapist and researcher at the AMC is she also lecturer in bachelor and post graduate physical therapy courses and member of the expert group of the Foundation for Patient and Family Centered Intensive Care (FCIC).

Currently, Juultje lives in Amsterdam with Dave Markus and their children Bas (1999) and Elfi (2004).

Name PhD student: Juultje Sommers
PhD period: January 2014 – June 2019
Name PhD supervisor: Prof. dr. F. Nollet
Prof. dr. R.H.H. Engelbert

1. PHD TRAINING

	Year	Workload (Hours/ECTS)
Courses		
· *Pubmed (e-learning).* AMC Medische bibliotheek	2013	3/0.1
· *Scientific writing in English for Publication*. AMC Graduate School	2013	42/1.5
· *Clinical Data management.* AMC Graduate School	2015	7.5/0.3
· *Basiscursus Regelgeving en Organisatie Klinische onderzoekers. (BROK).* AMC Graduate School	2016	28/1.0
Seminars, workshops and master classes		
· *Master class,"Klinische ergometrie met respiratoire gasanalyse bij patiënten met hartfalen".* NPI	2013	8/0.3
· *Open Space.* Family Centered Intensive Care (FCIC)	2014	6/0.2
· *Vroeg tijdig mobiliseren op de IC*. St. Elisabeth Ziekenhuis, Hill-Rom	2014	6/0.2
· *Interpretatie CPET*. The Physiology Academy	2015	8/0.3
· *Klinische inspanningsfysiologie*. Tulip Med academy	2015	8/0.3
· *Ronde Tafel bijeenkomst Expertgroep*. FCIC, Utrecht	2015	6/0.2
· *Van Kritiek ziekte naar goede Gezondheid*. AMC,KNGF, ELA	2018	8/0.3
Presentations (oral)		
Research meetings, department rehabilitation AMC		
· *PhD plan*	2014	14/0.5
· *CPET in the ICU, results*	2016	14/0.5
· *ICU-Mill, research proposal*	2016	14/0.5
· *ICU-Mill, results*	2017	14/0.5
Research meetings, department Intensive Care AMC		
· *Physical therapy in the ICU*	2017	14/0.5
Research meetings, HvA		
· *PhD plan*	2015	14/0.5
· *ICU-Mill*	2016	14/0.5

(Inter)national conferences (oral)

· *Mobiliseren en activeren van IC patient. AMC conference "IC in beweging".* Revalidatie AMC	2013	14/0.5
· *Evidence Statement: Fysiotherapie bij IC patiënten. AMC conference "IC in beweging*". Revalidatie AMC	2013	14/0.5
· *Ervaring van een IC patiënt. AMC conference "IC in beweging".* Revalidatie AMC	2013	14/0.5
· *DEMMI.* 2rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, Athens	2014	14/0.5
· *Early rehabilitation in the ICU*. 9th world congress of the international society of physical rehabilitation medicine, Berlin	2015	14/0.5
· *Mobiliseren en activeren volgens de Evidence statement*. Symposium "Mag ik deze dans van u". St Antonius	2015	14/0.5
· *Exercise physiology in critically ill patients*. 3rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, Copenhagen	2015	14/0.5
· *Vroege revalidatie bij IC patiënten*. Venticare	2016	14/0.5
· *Implementatie evidence statement voor fysiotherapie op de IC*. NVZF	2016	14/0.5
· *Korte en lange termijn gevolgen van multi-orgaan Falen.* RGF N-H.	2017	14/0.5
· *Workshop Intensive Care- After Care. APCPRA, China*	2017	14/0.5
· *ICU-Mill.* IXA award. VUMC	2017	14/0.5
· *Stappen naar herstel.* Dag van de fysiotherapie, KNGF	2017	14/0.5
· *Van Kritiek ziekte naar goede Gezondheid.* AMC,KNGF, ELA	2018	14/0.5
· *BWSTT*. Amsterdam Movement science (AMS), Arena Amsterdam	2018	14/0.5
· *ICU-Mill*. ESPRM, Vilnius	2018	14/0.5
· *Treadmill walking.* 6rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, Leuven	2018	14/0.5

Presentations (poster)

· *DEMMI*. 2rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients-Athens	2014	14/0.5
· *DEMMI*. ESICM, Brussel	2015	14/0.5
· *Evidence Statement.* ESICM, Brussel	2015	14/0.5

· *BWSTT*. 5rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, London	2017	14/0.5
· *BWSTT*. Dag van de fysiotherapie, KNGF	2017	14/0.5
· *BWSTT.* WCPT, Cape town	2017	14/0.5
· *BWSTT*. Amsterdam Movement science (AMS), Arena Amsterdam	2018	14/0.5

Attended (Inter)national conferences

· AMC-conference "IC in beweging, AMC (organization & attendance)	2013	48/1.7
· 1rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, Vienna	2013	16/0.6
· 2rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients-Athens	2014	16/0.6
· 3rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients-Copenhagen	2015	16/0.6
· 9th world congress of the international society of physical rehabilitation medicine, Berlin	2015	24/0.9
· 4rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients-Hamburg	2016	16/0.6
· 5rst European Conference on International early mobilization network Weaning & Rehabilitation in Critically ill Patients, London	2017	16/0.6
· Venticare, Utrecht	2016	8/0.3
· NVZF congres, Hilversum	2016	8/0.3
· West China International Forum Pulmonary Rehabilitation and Critical Care, Chengdu	2017	16/0.6
· Van Kritiek ziekte naar goede Gezondheid. AMC,KNGF, ELA	2018	8/0.3
· IC ventilatie symposium "Closed loop 2.0", Hamilton, AMC	2018	8/0.3

Other

2. TEACHING

	Year	Workload (Hours/ECTS)
Lecturing		
· Nederlandse "Evidence Statement Fysiotherapie op de IC" Waar staan we?, Cursus NPI "fysiotherapie op de IC afdeling", NPI	2013	3/0.1
· Fysiotherapie op de IC. Intensivisten inwerk programma, AMC	2013-2016	12/0.4
· Klinische lessen op de IC, AMC:		
• Mobiliseren	2012	3/0.1
• Demmi onderzoek,	2013	3/0.1
• Bedfiets onderzoek	2014	3/0.1
• Lopende band	2016	3/0.1
• Sara Combilizer	2017	3/0.1
• Implementeren bedfiets	2017	3/0.1
· Hoorcollege "fysiotherapie op de IC". HVA	2015, 2017	12/0.4
· Cursus coördinator en het geven van 8 presentaties: "fysiotherapie op de IC afdeling". NPI	2015, 2017, 2018	84/3.0
· Cursus coördinator en het geven van 1 workshop: Masterclass "Fysiotherapeutische interventies bij beademde (en weanende) ICU acquired weakness patiënten. NPI	2016, 2017	56/2.0
· Scholing klinimetrie en loopband. OT team Revalidatie, AMC (2x)	2017	8/0.3
· Scholing revalidatie: PICS.AMC	2018	3/0.1
· Scholing Evidence statement. Haaglanden	2018	3/0.1
· Cursus coördinator en het geven van 3 presentaties: "inspanningsfysiologie en trainingsleer bij de ziekenhuis patiënt". NPI	2018	28/1.0
Tutoring, Mentoring		
· Bachelor thesis (Physical therapy) DEMMI	2013	28/1.0
· Master thesis (Physical therapy) DEMMI	2013	28/1.0
· Master thesis (Physical therapy) CPET	2015	28/1.0
· Bachelor thesis (Physical therapy) EMG	2015	28/1.0
· Master thesis (Physical therapy) BWSTT	2016	28/1.0

Other

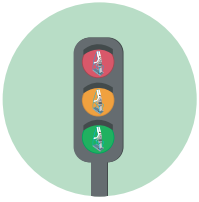
· E-learning, fysiotherapie op de IC. ESP, HvA	2015	28/1.0
· *Post-ICU challenge*. Hardloop wedstrijd organiseren en begeleiden van bachelor studenten (3x)	2016-2018	84/3.0
Total	**1249/44.6**	

	Year
Awards and Prizes	
· Innovation ICU-Mill. Amsterdam Science & Innovation Award, IXA	2017
· The best 3 Pitches from PhD students, ICU-Mill. ESPRM, Vilnius	2018

4. PUBLICATIONS

	Year
· Fysiotherapie op de IC. A&I, 2013	2013
· POEM: A Physical Therapist-Established Intensive Care Unit Early Mobilization Program: A Quality Improvement Project for Critical Care at the University of California San Francisco Medical Center. Fysiopraxis 2013	2013
· Evidence statement voor fysiotherapie op de intensive care. 2015, BohnStafleu van Loghum	2015
· Protocollen voor de intensive care. hst39: Mobiliseren van intensive care patiënten, de Tijdstroom	2015
· Casus: impact van een intensive care opname. Fysiopraxis 2016	2016
· POEM: The de Morton Mobility Index Is Feasible, Reliable, and Valid in Critically Ill Patients. Fysiopraxis 2016	2016
· Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. Ann Intensive Care 2017	2017
· POEM: Body weight-supported bedside treadmill training facilitates ambulation in ICU patients: An interventional proof of concept study. fysiopraxis, 2018	2018
· Early prediction of intensive care unit acquired weakness: a multicenter external validation study. J Intensive Care Med. 2018	2018

Contribution of authors



Chapter 2: Juultje Sommers, Raoul H.H. Engelbert, Daniela Dettling-Ihnenfeldt, Rik Gosselink, Peter E. Spronk, Frans Nollet, Marike van der Schaaf. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clinical Rehabilitation 2015; 29;1051-1063. JS and MvdS were responsible for the conceptualization and design of the study. JS was responsible for the conduct of the study, interpretation of the data and drafting the manuscript. DD, RG, PES, MvdS contribute to the interpretation of the data. MvdS coordinate the study and reviewed the manuscript and it revisions. FN, RHEE and MvdS study reviewed the final version of the manuscript. All authors read and approved the final manuscript.

Chapter 3: Juultje Sommers, Tom Vredeveld, Robert Lindeboom, Frans Nollet, Raoul H.H. Engelbert, Marike van der Schaaf. de Morton Mobility Index Is Feasible, Reliable, and Valid in Patients With Critical Illness.Physical Therapy 2016; 96;10: 1658-1666. JS, TV, RHHE and MvdS, provided concept, idea and research design. All authors provided writing. JS and TV provided data collection. JS, TV, RL, RHHE and MvdS provided data analysis. RHHE and MvS provide project management. MvdS provided fund procurement and institutional liaisons. RL, RHHE and MvdS provided consultation (including review of manuscript before submission). JS and TV were responsible for drafting and revision of the manuscript. RHEE and MvdS contributed to the revision of the manuscript.

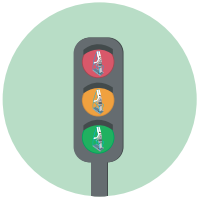
Chapter 4: Juultje Sommers, Emily Klooster, Siebrand B. Zoethout, Huub L.A. van den Oever, Frans Nollet, Robert Tepaske, Janneke Horn, Raoul H.H. Engelbert, Marike van der Schaaf. Feasibility of exercise testing in patients who are critically ill: a prospective, observational multicenter study. Archives of Physical Medicine and Rehabilitation 2018; https://doi.org/10.1016/j.apmr.2018.07.430. JS assisted in the design of the study, conducted the study in AMC, analyzed and interpreted the data, drafted the manuscript and was responsible for revision of the manuscript. EK conducted the study in Deventer hospital, analyzed and interpreted the data, and drafted the manuscript. SBZ and HLAvdO assisted in conducting the study in Deventer hospital and reviewed the final version of the manuscript. RT assisted in the design and assisted in conducting the study in AMC. JH assisted in the data analysis and reviewed the manuscript. FN and RHHE assisted in design of the study and reviewed the final version of the manuscript. MvdS conceived the study, participated in its design and coordination, assisted in the data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

Chapter 5: Juultje Sommers, Michelle van den Boorn, Raoul H.H. Engelbert, Frans Nollet, Marike van der Schaaf, Janneke Horn. Feasibility of muscle activity assessment with surface electromyography during bed cycling exercise in ICU patients. Muscle & Nerve

2018; doi: 10.1002/mus.26330. JS designed the study, conducted the study, analyzed and interpreted the data, and drafted the manuscript and the revisions. MvdB conducted the data analysis in MATLAB. MvdS, FN and RHHE designed the study and reviewed the final version of the manuscript. JH conceived the study, participated in its design and coordination, assisted in the data analysis and reviewed the manuscript. All authors read and approved the final manuscript

Chapter 6: Juultje Sommers, Denise Wieferink, Dave A. Dongelmans, Frans Nollet, Raoul H.H. Engelbert, Marike van der Schaaf. Body weight-supported bedside treadmill training facilitates ambulation in ICU patients: An interventional proof of concept study. Journal of Critical Care 2017;41:150–155. JS and DCW assisted in the design of the study, conducted the study, analyzed and interpreted the data, and JS drafted the manuscript. DAD assisted in the design and assisted in conducting the study. FN and RHHE assisted in design of the study and reviewed the final version of the manuscript. MvdS conceived the study, participated in its design and coordination, assisted in the data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

Dankwoord



Waar was ik aan begonnen? Promoveren? Nu is het dan zover, ik heb de stap gezet en mijn promotietraject is met dit proefschrift afgerond.

Wat mag ik mij gelukkig prijzen met alle mensen die mij hebben gesteund in mijn proces naar het definitieve eindresultaat. Graag wil ik deze personen dan ook persoonlijk bedanken.

Allereerst wil ik alle patiënten van de Intensive Care (IC) en Medium Care (MC) bedanken, die aan de onderzoeken hebben meegewerkt om mijn vraagstukken voor de verbetering van de (fysiotherapeutische) patiëntenzorg hebben weten om te zetten in het aangaan van een promotie traject.

Daarnaast was daar het promotieteam. Dit team gaf mij, in de wetenschap van zowel mijn kwaliteiten, als mijn onbekwaamheden, het vertrouwen en de kracht om aan dit promotietraject te beginnen. Samen zijn we op pad gegaan. Op deze weg hebben we samen genoten van de supersnelle data verzameling die we binnen mijn klinische werkzaamheden hebben gerealiseerd. Prachtig om zo de kwaliteit van de patiëntenzorg te kunnen verbeteren en daarbij direct je data te kunnen verzamelen. Ik bedank het promotieteam voor de inhoudelijke en taalkundige ondersteuning bij de mooie publicaties die wij met elkaar hebben weten te realiseren. Ik ben er trots op!

Mijn promotor, Prof. dr. F. Nollet. Frans, bedankt voor jouw analytisch vermogen, je duidelijke verwoording van conclusies en verbanden. Jij wist mij op een creatieve wijze te inspireren en mede daardoor tot dit mooie eindproduct te komen. Tevens gaf je mij het vertrouwen dat ik met iets waardevols bezig was.

Mijn promotor, Prof. dr. R.H.H. Engelbert. Raoul, bedankt voor jouw altijd positieve inzet, je menselijke benadering en de zorg om mijn proces. Dank ook voor je creatieve oplossingen om op het gebied van de Engelse taal het beste in mij boven te halen.

Mijn co-promotor, dr. J. Horn**.** Janneke, bedankt voor de vele uren samen knutselen aan een artikel en daarbij jouw kritische kijk op de uitkomsten van het fysiotherapeutisch onderzoek. Daarvan heb ik geleerd hoe waardevol het is om, een met passie vervuld proefschrift, goed te kunnen beschouwen. Jouw praktische en concrete aanpak paste goed bij mij. Het was een fijne ervaring en het zorgde ervoor dat de trein bleef rijden.

Mijn co-promotor, Associate Prof. dr. M. van der Schaaf. Marike, bedankt dat je een co-promotorschap durfde aan te gaan met iemand die je al jaren vanuit het werk en privé goed kent. Ik heb mij vooraf afgevraagd of een bestaande vriendschap een goed promotieproces niet in de weg zou staan. In onze jonge jaren, als beginnende fysiotherapeuten op de IC zijn we ooit gestart met een samenwerkingsverband. Ons “IC-dagboekje” met onwetende

en nieuwsgierige vragen is uiteindelijk uitgemond in jouw associate professorschap en uiteindelijk ook in deze promotie. Onze samenwerking bleek dus niet alleen in de praktijk, maar ook op wetenschappelijk gebied een goede match. 'Eén plus één werd op deze manier drie' en daar ben ik heel blij mee! Marike, bedankt!

En dan niet te vergeten,
De leden van de promotiecommissie, Prof. M.A. Boermeester, Prof. N. Juffermans, Prof. J.M. Prins, Prof. C. Veenhof, Prof. R. Gosselink en Prof. H. Stam. Bedankt voor het lezen en beoordelen van het proefschrift.

Alle co-auteurs. Ik wil hen van harte bedanken voor de goede samenwerking, de input en feedback op de conceptartikelen. Aangezien alle artikelen met een grote verbondenheid, gericht op de patiëntenzorg tot stand zijn gekomen, zijn ook alle co-auteurs nauw bij het gehele proces van onderzoek tot aan het uiteindelijke artikel betrokken geweest. Het was voor mij een bijzondere ervaring om dit alles zo met elkaar te delen en gelukkig is onze samenwerking, ook na het voltooien van mijn proefschrift, nog lang niet afgelopen.

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"Last but not least".

Mijn gezin

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