

Early Physiotherapy in the Neurointensive Care Unit

Passive Physiotherapy Interventions

Anneli Thelandersson

Department of Anaesthesiology and Intensive Care
Institute of Clinical Sciences
Sahlgrenska Academy at University of Gothenburg



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anneli.thelandersson@vgregion.se

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*The size of your dreams must always exceed your current capacity to achieve them.
If your dreams do not scare you, they are not big enough.*

Ellen Johnson Sirleaf

To Jakob and Ruth my wonderful children

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Göteborg, Sweden

ABSTRACT

Background: In critically ill patients, treated in the neurointensive care unit (NICU) because of severe brain injury or stroke, physical activities have been restricted to a minimum due to the potential risks of complications and adverse events. Nevertheless, passive physiotherapy treatments are widely used without conclusive evidence for their safety.

Aim: The overall aim of this thesis was to investigate if three different passive physiotherapy interventions i.e. prone position (PP), passive range of motion (passive-ROM) and continuous passive motion (CPM), were safe to use in patients that are critically ill due to severe brain injury or stroke when admitted to a NICU and to investigate the respiratory and circulatory effects of these interventions.

Methods: This thesis consists of four different quantitative research papers. Paper **I** investigated the effect of PP on lung oxygenation as well as the intracranial and systemic haemodynamic variables before, during and after PP. Paper **II** investigated the intracranial, cerebrovascular and systemic haemodynamics before, during and after a session of passive-ROM as performed in clinical practice. Paper **III** studied peripheral blood flow velocity (PBFV) and resistance index (RI) before, directly after and after a passive-ROM intervention. In paper **II** and **III** a healthy control group matched for age and sex was also included. Paper **IV** studied intracranial and systemic haemodynamics before, during and after a session of 20 minutes of CPM with a bedcycle ergometer.

Main results: I. PP enhanced oxygenation without any significant changes in intracranial pressure (ICP), cerebral perfusion pressure (CPP) or blood

pressure (BP) while heart rate (HR) increased. **II.** During passive-ROM CPP, BP and HR did not change significantly, while ICP decreased after passive-ROM. Furthermore, no significant changes in cerebral blood flow velocity or pulsatility index (PI) were noted. In the healthy control group, a significantly higher BP was found before the intervention, but no other significant results were noted. **III.** Passive-ROM interventions did not significantly affect PBFV or RI. When comparing the patient group with the control group in paper II and III, a significantly higher PI and PBFV and a lower RI were noted in the patient group. **IV.** CPM did not affect ICP but significantly increased BP and stroke volume (SV) during the exercise. Furthermore, cardiac output, SV, BP and CPP were increased during versus after the intervention.

Conclusion: Prone position, passive-ROM and CPM are safe to use in critically ill patients, suffering from brain injuries or stroke treated in the NICU, since the intracranial and systemic haemodynamic responses are small. PP increased the oxygenation in this patient group.

Keywords: physiotherapy, brain injury, stroke, intensive care units, prone position, range of motion, continuous passive motion, intracranial pressure, cerebral perfusion pressure, haemodynamics

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: På grund av den eventuella risken för komplikationer i samband med fysioterapeutiska behandlingar av svårt skallskadade patienter inom neurointensivvården har dessa inte varit så omfattande. Passiva behandlingsmetoder används dock, utan tillräckliga bevis för deras säkerhet.

Syfte: Det övergripande syftet med denna avhandling var att undersöka patientsäkerheten av tre olika fysioterapeutiska behandlingsmetoder; bukläge, passiv rörelseträning och sängcykling, när de används i ett tidigt skede efter en svår skallskada som kräver intensivvård. Vidare undersöktes effekten av dessa behandlingar på blodcirkulation eller respiration.

Metod: Avhandlingen består av fyra delarbeten. I arbete **I** undersöktes säkerheten och effekten av bukläge genom att låta patienterna ligga på mage i tre timmar. Före, under och efter bukläget undersöktes intrakraniella, cirkulatoriska och respiratoriska variabler. I arbete **II** undersöktes säkerheten och den cirkulatoriska reaktionen på passiv rörelseträning för armar och ben. Före, under och efter en session av passiv rörelseträning, som den utförs i kliniken, undersöktes intrakraniella och cirkulatoriska variabler. I arbete **III** undersöktes den perifera cirkulatoriska reaktionen på passiv rörelseträning i ett ben. I arbete **II** och **III** inkluderades även en frisk kön- och åldersmatchad kontrollgrupp. I arbete **IV** undersöktes säkerheten och de cirkulatoriska reaktionerna på en session av 20 minuters sängcykling.

Resultat: **I.** Bukläge ökade syresättningen utan att de intrakraniella och cirkulatoriska variablerna förändrades, förutom att hjärtfrekvensen var något högre i bukläge. **II.** Passiv rörelseträning minskade det intrakraniella trycket i patientgruppen. Övriga cirkulatoriska variabler påverkades inte av passiv rörelseträning förutom att blodtrycket hos kontrollgruppen var högre före behandlingen och sjönk när denna påbörjades. **III.** Passiv rörelseträning i ett ben påverkade inte blodcirkulationen hos patientgruppen eller kontrollgruppen. Vid en jämförelse mellan patient- och kontrollgruppen i studie **II** och **III** sågs en högre cerebral resistans och en lägre perifer resistans i de undersökta blodkärlen med högre perifer blodflödes-hastighet i patientgruppen under passiv rörelseträning. **IV.** Under sängcykling ökade blodtrycket och hjärtats slagvolym jämfört med före. Hjärtats slagvolym, hjärtminutvolymen, blodtrycket och hjärnans perfusionstryck var också högre under cykling jämfört med efter denna.

Slutsats: En kortare tids bukläge, passiv rörelseträning och sängcykling är säkra behandlingsmetoder att använda i ett tidigt skede efter en svår skallskada som kräver intensivvård då de intrakraniella och cirkulatoriska reaktionerna var små. Blodcirkulationen i hjärnan och benen påverkades inte av passiv rörelseträning och bukläge ökade syresättningen i den här patientgruppen.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

- I. Thelandersson A, Cider Å, Nellgård B. Prone position in mechanically ventilated patients with reduced intracranial compliance. *Acta Anaesthesiol Scand.* 2006;50:937-41.
- II. Thelandersson A, Cider Å, Volkmann R. Cerebrovascular and systemic haemodynamic parameters during passive exercise. *Adv Physiother.* 2010;12:58-63.
- III. Thelandersson A, Volkmann R, Cider Å. Blood flow velocity and vascular resistance during passive leg exercise in the critically ill patient. *Clin Physiol Funct Imaging.* 2012;32:338-42
- IV. Thelandersson A, Nellgård B, Ricksten S-E, Cider Å. Effects of early bedside cycle exercise on intracranial pressure and systemic haemodynamics in critically ill patients in a neurointensive care unit. Submitted

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ABBREVIATIONS

BFV	Blood Flow Velocity
BP	Blood Pressure
CBFV	Cerebral Blood Flow Velocity
CFA	Common Femoral Artery
CO	Cardiac Output
CPM	Continuous Passive Motion
CPP	Cerebral Perfusion Pressure
FiO ₂	Fraction of Inspired Oxygen
HR	Heart Rate
ICP	Intracranial Pressure
ICU	Intensive Care Unit
MAP	Mean Arterial Blood Pressure
MCA	Middle Cerebral Artery
NICU	Neurointensive Care Unit
PaCO ₂	Arterial Partial Pressure of Carbon dioxide
PaO ₂	Arterial Partial Pressure of Oxygen
PBFV	Peripheral Blood Flow Velocity
PI	Pulsatility Index

RCT	Randomized Controlled Trial
RI	Resistance Index
ROM	Range of Motion
RPM	Revolutions per Minute
RR	Respiratory Rate
SaO ₂	Arterial Oxygen Saturation
SAP	Systolic Arterial Blood Pressure
SpO ₂	Peripheral Oxygen Saturation
SV	Stroke Volume
SVV	Stroke Volume Variation
TBI	Traumatic Brain Injury
TCD	Trans Cranial Doppler
VAP	Ventilator Acquired Pneumonia
WHO	World Health Organization

DEFINITIONS IN SHORT

Early	Before the expected or usual time (1)
Exercise	Physical activity that is planned, structured repetitive and purposive, in the sense that improvement or maintenance of one or more components of physical fitness is an objective (2)
Mobilize	Put into motion, circulation or use (1)
Physical activity	Any bodily movement produced by skeletal muscles that result in energy expenditure (2)
Physical fitness	A set of attributes that people have or achieve that relates to the ability to perform physical activity. To be physically fit is to have the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies (2)
Physical function	The capacity of an individual to carry out the physical activities of daily living (3)
Physical inactivity	An activity level insufficient to meet present recommendation (4)
Range of motion (ROM)	Range of rotation or translation through which a joint is actively or passively moved between two extreme positions in a certain direction. The ROM is quantified in degrees or millimeters (5)

1 INTRODUCTION

1.1 Intensive care

The need to closely look after patients that are most critically ill is not a novel requirement. As early as the 1850s, Florence Nightingale placed these patients nearest the nursing station to be able to watch them more closely. By doing so, she focused very early on a separate area for the most critically ill. The concept of specialized intensive care units for patients with respiratory problems started to develop first in the 1950s as a consequence of a polio epidemic in Copenhagen (6, 7).

During an admission to the Intensive Care Unit (ICU) due to critical illness, patients spend most of their time in bed and are often on mechanical ventilation (8-10). A study showed that patients in an ICU spend more than 7 out of 8 hours during the day in bed with minimal or no activity at all. Patients who were awake and cooperative and not on mechanical ventilation were more likely to be active or activated and the patients that were sedated or extremely agitated were less likely to get out of bed, irrespective of mechanical ventilation. They also found that the patients spend at least one third of the 8 hour day alone (8). Since patients admitted to ICUs are bed-bound for most of the stay, often on mechanical ventilation and also sedated and/or comatose - large changes may be seen in, among others, the respiratory, musculoskeletal and cardiovascular systems (10-13).

1.2 Impact of intensive care on different body-systems

1.2.1 Respiratory system

The respiratory system is greatly affected by mechanical ventilation and anaesthesia as well as bed rest and immobility (14, 15). Gas exchange in the lungs gets impaired by anaesthesia (16) and the most common cause of gas exchange impairment are a displacement of the diaphragm which leads to a decrease in functional residual capacity, the development of atelectasis and ventilation/perfusion mismatch. These complications lead to impaired oxygenation, hypoxic events and in combination with the underlying cause of

admission to the ICU may also increase the risk of ventilator acquired pneumonia (VAP) and acute respiratory distress syndrome (ARDS) (14-22). ARDS is a severe complication with a mortality rate of 40-50% (23, 24). Patients surviving ARDS have an increased risk of long-term complications such as decreased muscle and physical function, depression, post-traumatic stress disorders (PTSD), anxiety and cognitive difficulties (25-29).

1.2.2 Cardiovascular system

A stay in the ICU has substantial effects on the cardiovascular system. It leads, amongst other things, to an increase in heart rate (HR), a decrease in stroke volume (SV) and a loss of cardiac muscle mass. It appears as though the heart reacts to inactivity in the same way as skeletal muscles with hypotrophy as a consequence. There is also a decrease in blood volume, reduced red blood cell mass, a promotion of venous stasis and damage to the vascular endothelium through compression of the veins by long contact with the bed, orthostatic intolerance and increased risk for venous thrombosis (11, 12, 14, 30).

1.2.3 Muscular and mental system

ICU patients can also develop hypotrophy with reduced strength and endurance in skeletal muscles and tendons, contractures in joints, bone loss and a degeneration of cartilage (11, 13, 14, 31-33).

In ICU survivors, a lower quality of life, depression and PTSD have been described (34, 35). Depression is very common and can be seen in as many as 33% of the patients up to 12 months after discharge. This depression is mainly caused by somatic symptoms due to the physical disabilities the patients have developed during their ICU stay (35).

There are complications of other body-systems as well, such as the renal, skin, nervous, immune, gastrointestinal and metabolic systems (12, 14, 36).

All these complications can result in a decreased capacity to adequately respond to physical activity, which can lead to a prolonged hospital stay, a risk for sustained morbidities after hospital discharge and finally, increased mortality (11, 12, 14, 30, 34).

1.3 Physiotherapy

Physiotherapy is the third largest health profession after nurses and physicians in both Sweden and the Western world. It is an academic subject as well as a professional field of work. Physiotherapy as a profession is based on specific knowledge, higher education and with an independent professional responsibility for the good of the individual, as well as for the greater good, ethical rules and with its own responsibility for knowledge development and research within the field (37).

According to the World Confederation for Physical Therapy, “physical therapy provides services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by ageing, injury, pain, diseases, disorders, conditions or environmental factors. Physical Therapy is concerned with identifying and maximizing quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation. This encompasses physical, psychological, emotional and social wellbeing” (38).

1.4 Physical activity and exercise

The World Health Organization (WHO) defines physical activity according to Caspersen et al. (2) as “any bodily movement produced by skeletal muscles that require energy expenditure – including activities undertaken while working, playing, carrying out household chores, traveling and engaging in recreational activities”. Physical inactivity is identified as one of the ten leading risk factors for global mortality and is rising in many countries (39). Lee et al. defined in 2012 physical inactivity as “an activity level insufficient to meet present recommendation” i.e. the recommendations on physical activity by the WHO (4).

Physical activity for adults as recommended by the WHO (39) is:

- At least 150 minutes of moderate-intensity physical activity throughout the week, or do at least 75 minutes of vigorous-intensity physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity

- For additional health benefits, adults should increase their moderate-intensity physical activity to 300 minutes per week, or equivalent
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week

A subcategory of physical activity is exercise that, according to Caspersen et.al. (2) is defined as “physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective.” Physical fitness is a set of attributes that people have or achieve and to be physically fit is defined as “the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies”(2).

There is no definition that encompasses the passive interventions used by physiotherapists such as passive range of motion (passive-ROM), continuous passive motion (CPM) or passive ambulation to a wheelchair. Often this type of intervention is defined as passive exercise even though by definition it is not entirely correct. Physiotherapy interventions for the most critically ill often start with passive interventions and moves to active exercise when the patient is able to do so. The word exercise when used in this thesis encompasses both active and passive exercise even if it by definition is not entirely correct.

1.5 Physiotherapy in the ICU

Physiotherapists in the ICU need to be a member of the multi-professional team that is involved in the care of patients that are critically ill and admitted to an ICU (40, 41). Even as early as the 1950s, when the first intensive care units developed in Copenhagen, a physiotherapist was involved in patient care, to enhance survival rates. At that time teamwork was already an important factor for high-quality intensive care (6).

In 2008, the European Respiratory Society and European Society of Intensive Care Medicine Task Force identified several important areas for physiotherapists working with patients in the ICU (40). These areas were: physical deconditioning, neuromuscular and musculoskeletal complications, prevention and treatment of respiratory conditions and emotional problems

and communication. Physiotherapy interventions when appropriately prescribed with the right therapy for the right patient may improve outcomes and reduce the risks of intensive care as well as its cost (40, 42). The only intervention found so far to improve physical function in ICU survivors is exercise, and Calvo-Ayala et al. concluded that the effect is supposedly greater the earlier exercise begins (43).

1.5.1 Physiotherapy interventions in the ICU

There is no clearly defined term that is used to describe the different interventions used in order to get the patients more active in the ICU. Different authors use different terms to describe the intervention used and studied. The most common terms are mobilization, mobility, exercise, activity and rehabilitation and there is often a prefix of “early” before the term for example early mobilization (31, 44-47). Early mobilization seems to be the most used term and often encompasses both passive and active interventions (46, 48, 49). The term early is not clearly defined, but according to Collins English dictionary it is defined as “before the expected or usual time” (1). In ICU research it could be anything from within the first 72 hours and up to 2 weeks after ICU admission (31, 50). In this thesis, when referring to a research-paper the term used in that paper to describe the intervention studied is the one used here too, otherwise early mobilization is the term used.

Early mobility and ambulation in hospitalized patients were reported as early as during World War II, as a way to rapidly get soldiers back into battle (51). In the ICU, early ambulation was reported for the first time in the seventies, where two reports describing the ambulation of patients that were mechanically ventilated when admitted to an ICU were published (52, 53). A real breakthrough for early mobilization in the ICU worldwide came in 2007 when Bailey et al. and Morris published their reports about early activity in critically ill patients (44, 54). Since then, several reports have been published addressing this important subject and the positive effects of early mobilization of critically ill patients (31, 46-48, 55-58).

The physiotherapy treatments used in the ICU are sub-divided into passive and active interventions. Passive interventions used are positioning, passive-ROM, stretching, CPM, electrical muscle stimulation and splinting. The active interventions are exercise therapy, activities of daily living training as balance and standing, and out of bed mobilization (41, 59-61).

1.5.2 Safety and feasibility

Several studies during the last decade have shown the safety and feasibility of early physiotherapy interventions and mobilization for patients who are critically ill and on mechanical ventilation. Physiotherapy interventions and mobilization can be started early after ICU admission (44, 58, 62-65). A study investigating the patient safety of early mobilization for patients with femoral catheters found no catheter related adverse events (45). When utilizing early mobilization during continuous renal replacement therapy no adverse events were found, nor did any filter occlusion or failure occur (49). Furthermore, no complications during early mobilization in patients on extracorporeal membrane oxygenation have been seen (66). Thus, physiotherapy in the ICU is considered a safe procedure with very few adverse events occurring during therapy sessions (44, 49, 62, 64, 67). The most common adverse events noted during early physiotherapy interventions in the ICU are patient-ventilator asynchrony and agitation (58, 62).

1.5.3 Effects of physiotherapy interventions

Early physiotherapy and thereby early mobilization in the ICU has been proven to give advantages to both patients and society. Several studies have reported the positive effects of early mobilization such as: decreased ICU and hospital length of stay, increased discharge to home, decreased hospital acquired infections, improved quality of life, enhanced muscle strength, shorter time of delirium, more ventilator free days and reduced costs (31, 42, 46-48, 58, 65, 68, 69). The lack of early ICU mobility is a factor associated with readmission and death during the first year after ICU admission (56).

1.5.4 Considerations when treating patients that are critically ill

Physiotherapy interventions in the ICU may be complicated to perform due to the patient's critical respiratory and circulatory condition, but also because of necessary medications administered and invasive monitoring. Due to their critical illness, the patient's condition can rapidly deteriorate so monitoring of the patient's vital parameters during physiotherapy interventions is of utmost importance. Before commencing any physiotherapy intervention, the patient has to be screened for potential absolute contraindications and relative contraindications, making a risk-assessment prior to every treatment to evaluate potential risks and benefits (60).

The variables that are most important to be taken into consideration are listed in *Table 1*.

Table 1. The most important variables to be taken into consideration before commencing early mobilization of a critically ill patient in an ICU.

Heart rate	<40 and >130 beats/minute Recent myocardial ischemia
Blood pressure	Mean Arterial Blood Pressure <60 mmHg and >110 mmHg
Oxygen saturation	≤ 90%
Ventilatory settings	Fraction of Inspired Oxygen ≥ 0.6 Positive End Expiratory Pressure ≥ 10 cmH ₂ O
Respiratory rate	>40 breaths/min
Level of consciousness	Richmond Agitation Sedation Scale -4, -5, 3, 4
Inotropic support	Dopamine ≥ 10 µg/kg/min Nor/adrenalin ≥ 0.1 µg/kg/min
Body temperature	≤ 36°C and ≥ 38.5°C
Neurologic instability	Intracranial pressure ≥ 20 cmH ₂ O
Clinical view	Decreased level of awareness/consciousness Sweating Abnormal face-color Pain Fatigue
Unstable fractures	
Lines	Presence of lines that make mobilization unsafe

Adapted from Sommers et. al. (60)

1.5.5 Barriers to physiotherapy in the ICU

Even though early physiotherapy interventions induce many positive effects and are considered an important aspect in the care of the critically ill, there are barriers from other ICU staff against these interventions. The most commonly existing barriers are, according to the staff: the culture of the unit, communication difficulties, lack of personnel and equipment resources, risk of disconnection or displacements of lines, sedation and the risk of injury to themselves (70-73). The level of patient mobilization in the ICU is dependent on the profession of the health care provider. A study has shown that physiotherapists mobilize patients to a much higher level than registered nurses do (74). When comparing the same group of patients the physiotherapists limited the patient's mobility to in-bed treatment in 37% of the cases compared to 73% of cases by nurses. The physiotherapist also mobilized the patients to standing and ambulating in 38% of the cases while nurses did this in 13% of the cases (74).

1.5.6 Physiotherapy in a Swedish ICU

In Sweden, a majority of the ICUs have a physiotherapist working in the ward as a member of the multi-professional team around the patients that are critically ill. They do not need a referral from a physician and are very independent in their occupational work. Early physiotherapy interventions are not a new phenomenon for patients in an ICU in Sweden. It has been used for decades with good clinical experiences and nowadays it is included in the standard care of ICU patients.

1.6 Neuro intensive care unit (NICU)

In Sweden, there are six hospitals with special neurointensive care units: Skåne University Hospital in Lund, Linköping's University Hospital, Karolinska University Hospital in Stockholm, Akademiska Hospital in Uppsala, Norrland's University Hospital in Umeå and Sahlgrenska University Hospital in Gothenburg.

The NICU at Sahlgrenska University Hospital is an 8 bed ward with a ratio of 2:2 in nurses/assistant nurses and patients and an inclusion area of 1.9 million inhabitants. The ward is run by an anaesthetist and neurosurgeons and neurologists are present at the ward every day, other specialists are on consultation basis. The staff consists of nurses that are specialized in intensive care and assistant nurses. Physiotherapists are on duty every weekday and in special cases even on weekends. The ward admits about 460 patients per year, 360 of those being ICU patients and the others being post-operative patients. The most common diagnoses amongst the ICU patients at the ward are subarachnoid haemorrhage (about 100 patients), trauma (about 80 patients) and cerebrovascular diseases (haemorrhage and infarction, about 80 patients).

Compared to when treated in an ICU, a treatment in a NICU for patients with brain injuries or stroke is associated with improvement in outcome/s, reduced mortality rate, reduced length of intensive care need, improved resource utilization and fiscal benefits (75-77). Higher hospital volume i.e. larger numbers of ICU beds and admissions are associated with improved outcome/s and reduced mortality for the patients and might be one explanation for the lower mortality rate and better outcome for patients in a NICU (76). A neurointensivist present at the ward may also reduce hospital and NICU stay, improve outcome/s, reduce mortality and result in financial

benefits (78-80). The multi-professional team in an NICU who are skilled at monitoring, detecting and treating neurological complications might also be an explanation for the good outcome in NICU units (76).

1.6.1 Environment and treatment

In the NICU, the environment is very *high tech* and the patients are connected to a range of tubes and lines for respiratory and circulatory support and control. For the patients this means advanced pharmacological treatments often in combination with surgery and they are often on mechanical ventilation. Monitoring of the intracranial pressure (ICP) and cerebral perfusion pressure (CPP) is of utmost importance in the most critically ill, as it guides the therapy. Other vital parameters that are monitored are HR, blood pressure (BP) and oxygen saturation (81-84)

The main goals for the treatments in NICUs are to prevent the worsening of the primary injury to the brain and to avoid secondary complications (84). Patients are meticulously monitored and treated to avoid hypoxia, hypotension, fever, anemia, high ICP and a low CPP since these are all associated with poor outcome/s (82, 85).

1.6.2 Diagnoses

Some of the most common diagnoses in the NICU are intracerebral haematomas, subarachnoid haemorrhage, stroke and traumatic brain injury (TBI). TBI is an umbrella term for different kinds of injuries that can appear after trauma to the brain. There is often a mix of more than one injury involved in TBI as subdural haematoma, epidural haematoma, traumatic subarachnoid haemorrhage, contusions and diffuse axonal injuries. In TBI there may also be fractures to the skull or the base of the skull (84, 86). Trauma to the brain is a multidisciplinary injury requiring pre-hospital and emergency department care as well as specialties as neurosurgery, intensive care, neuroradiology, other surgical disciplines and rehabilitation (87).

Other, quite common, diagnoses that can be seen in an NICU are spinal cord injuries, epilepsy, Guillain-Barre's syndrome and myasthenia gravis (84, 88).

1.6.3 NICU vs. ICU

One out of 5 patients in an ICU is on mechanical ventilation due to a neurological disease. These patients are on mechanical ventilation for longer

periods than other ICU patients and more often receive a tracheostomy. They also have a longer ICU and hospital stay and a higher mortality rate despite fewer extra-cerebral organ dysfunctions, except for VAP in patients with brain trauma (89).

Differences between patients treated in NICU vs. those treated in the ICU (90):

- Longer hospital stay
- More tracheostomies
- More invasive haemodynamic monitoring
- Less intravenous sedation
- Fewer blood transfusions
- More enteral and parenteral nutrition

1.6.4 Physiotherapy in the NICU

Before commencing physiotherapy interventions with patients in an NICU the same variables as for any patient in a medical or surgical ICU have to be considered. However, there is also a range of other specific considerations for the physiotherapist to consider in a NICU. In the acute phase after a brain injury or stroke, the cerebral autoregulation i.e. the cerebral blood vessels ability to maintain a constant cerebral blood flow by dilating or constricting can be impaired, making the cerebral blood flow pressure-dependent. As a result, a decrease in BP could contribute to cerebral ischemia and an increase could raise the ICP due to an increased cerebral blood volume (91). In patients with an aneurysmal subarachnoid haemorrhage physiotherapists must also consider the risk of re-bleeding, hydrocephalus, seizure and vasospasm (92, 93). The patient safety as well as the safety for the staff could also be at risk in patients with hemiparesis, hemiplegia and cognitive impairment (94).

Due to the risks of complications and adverse events when treating patients that are critically ill due to severe brain injury or stroke, physical activities have historically been restricted to a minimum. Despite the haemodynamic, respiratory and other important characteristics able to compromise patient safety during early activity and mobilization interventions in the NICU, an increasing number of studies on its feasibility have recently been reported. The conclusion is that the positive effects of early activity interventions in the NICU outweigh the possible adverse events (47, 94-96).

The described beneficial effects of early activity interventions for patients in a NICU are an increased level of mobility, reduced length of hospital and NICU stay. The incidences of hospital acquired infections are also reduced (47, 94, 96). There is also evidence that passive-ROM of a paralyzed limb after a brain injury could improve functional recovery by a promotion of neural plasticity, and thereby rerouting signals in the injured area creating new connections (97).

A suggestion for a simplified model for progression of the physiotherapy interventions used for the critically ill patient in a NICU is listed in *Table 2*.

Table 2. A simplified model for progression of physiotherapy interventions in an NICU.

Stage	Intervention	Activity
1	Passive interventions in bed	Changing position in bed Head of bed elevation Passive-ROM Passive CPM
2	Active interventions in bed	Moving in bed Active ROM exercises Active CPM Sitting in bed Sitting on the edge of the bed
3	Activities out of bed	Stand beside of the bed Stand and pivot to chair
4	Ambulating	Walking with assistance Walking without assistance

ROM – range of motion, CPM – continuous passive motion

1.7 Passive interventions

1.7.1 Prone position

Prone position has been used for about four decades as a treatment to improve oxygenation for patients on mechanical ventilation in ICUs, with severe lung problems and a high oxygen demand (98, 99). Prone position enhances oxygenation in 58-100% of the patients (100, 101) and the improvement occurs most often within minutes and is mostly sustained when the patient is turned back into a supine position. The physiological cause of

the improvement in oxygenation is still not completely known (101). Studies of prone position have shown that the dorsal regions of the lungs are better aerated and less collapsed than in the supine position, lung perfusion is more evenly distributed, there are enhanced postural drainage of secretions and the shape of the lung is less affected by other organs (101-106). The effect of prone position on mortality has been debated, but recent literature indicates that periods of prone position reduce mortality (107-110). Prone position has been proven to be a safe treatment to enhance oxygenation in patients that are critically ill when admitted to an ICU and on mechanical ventilation (109-111). It is recommended to start prone position early in the cause of lung problems and to prioritize this intervention before other invasive treatments due to the relatively low risk of complications (103, 109, 110, 112). Additionally a 4 hour daily prone position has also been proven to reduce the incidence of lung deterioration in intubated comatose patients (113).

There is no consensus on how a patient should be placed when in prone position and different methods are used. There are two different positions that are predominantly used, a semi-prone position (where a 135° prone position is one method) and a total prone position. Both semi-prone positions with different angles and prone position are in literature described as prone position. In a semi-prone position you often use soft pillows as a way to place the patient in a good position. In the prone position you use special pillows or beds or devices to get a good position (109, 114-117).

In most of the earlier studies of prone position, patients with severe brain injuries or stroke were excluded (108, 112, 115). There is however, one retrospective study and one case report where patients suffering from subarachnoid haemorrhage were turned prone with good oxygenation results (118, 119).

1.7.2 Passive range of motion

For patients that are unable to move their arms and/or legs on their own due to coma and/or sedation, passive-ROM is a very common treatment (61). The definition of ROM is “range of rotation or translation through which a joint is actively or passively moved between two extreme positions in a certain direction” (5). For patients in an ICU, passive-ROM is performed manually by a physiotherapist (40, 61). The four main themes for doing passive-ROM are assessment, prevention, maintenance and restoration (120). During passive-ROM, the physiotherapist assesses the range of motion, muscle tone,

pain and neurological function (40, 120). Prevention, maintenance and restoration are aimed towards joint range of motion, soft-tissue extensibility, muscle strength and function and the prevention of thromboembolism and edema (61, 120).

Passive-ROM is commonly used by physiotherapists in ICUs but there is a wide range in its usage. When used, it is mostly performed 5-7 days a week, with 1-4 sets per joint and between 2-30 repetitions of every movement in each joint (121, 122). In clinical practice in the NICU at Sahlgrenska University Hospital, passive-ROM is performed 5 days a week, one set per movement per joint and between 3-10 repetitions per movement in patients without increased muscle tone and with an inability to move the limbs on their own.

There seem to be no reported data on the ability of this kind of passive-ROM to maintain joint range of motion or soft-tissue length, to maintain function or to decrease the circulatory risks (61, 123). However, longer periods of passive motion, CPM, performed by different devices have shown positive effects on muscles with higher specific force of the muscle fiber, pain and edema (124-126). There are, on the other hand, data on the safety of passive-ROM when performed in patients that are critically ill and admitted to ICUs (58, 124). Using passive-ROM for patients in a NICU has earlier been reported to be a safe intervention. (127, 128). However, those two studies were not conducted during a full session of passive-ROM as used in clinical practice. This concern was recently addressed, concluding that passive-ROM performed in patients with severe brain injuries or stroke is safe (129). There is however, to our knowledge, no study investigating the cerebral blood flow velocity (CBFV) and pulsatility index (PI) in a cerebral artery during a full session of passive-ROM in patients with severe brain injuries or stroke. Neither are there any studies investigating the peripheral blood flow velocity (PBFV) and resistance index (RI) in an artery in the leg during a passive-ROM exercise in patients that are critically ill.

1.7.3 Bedside cycle ergometry

One way of giving patients in ICUs longer periods of motion exercise is to use bedside cycle ergometry. There are bedcycles that could be used for both active and passive exercise. When used for passive exercise it is adjusted for revolutions per minute (RPM) and in case of active cycling there are different gears to use (31, 59).

Passive intervention with a bedside cycle ergometer is considered safe and feasible in the critically ill ICU patients since there are no clinically relevant and almost no significant changes in respiratory and circulatory variables as respiratory rate (RR), HR and BP during therapy sessions (31, 50). Starting this intervention as early as within 72 hours from ICU-admission has been proven to be safe and without any significant haemodynamic or respiratory changes (50).

When using bedside cycle ergometry for active exercise in critically ill cooperative patients in an ICU, only minor increases in HR and RR without any differences in BP or peripheral oxygen saturation (SpO₂) were noted. The therapy was also highly accepted by the patients and all of them wanted to do this activity during future physiotherapy sessions (130). An extra daily-session of passive and active bedside cycling exercise for the patients that are critically ill, showed an improved functional exercise capacity, muscle force and perceived functional status in these patients at hospital discharge (31).

However, there are no data on the effects of bedside cycle ergometry on intracranial and cerebral perfusion pressure and on systemic haemodynamic variables in patients with severe brain injuries or stroke when admitted to a NICU.

2 AIM

The overall aim of this thesis was to investigate if three different passive physiotherapy interventions were safe to use in patients who are critically ill due to severe brain injury or stroke when admitted to a NICU and/or to investigate the effect of the interventions.

The specific aims of the papers included in the thesis are:

- I. To investigate if prone position is a safe and useful treatment in patients with reduced intracranial compliance.
- II. To investigate the safety of passive range of motion with respect to intracranial, cerebrovascular and systemic haemodynamic parameters in critically ill with severe brain injury or stroke. Further, to compare the results to a healthy control group matched for age and sex.
- III. To investigate the effect of passive range of motion on arterial peripheral blood flow velocity and resistance index. Further, to compare the results to a healthy control group matched for age and sex.
- IV. To investigate if early mobilization with a bedside cycle ergometer is safe and feasible for patients that are critically ill due to severe brain injury or stroke.

3 PATIENTS AND METHODS

This thesis is based on four papers using quantitative research methodology. In *Table 3* a research design overview is shown.

Table 3. Research design overview

Study	I	II	III	IV
Aim	Circulatory and respiratory variables during prone position	Cerebrovascular and systemic haemodynamic variables during passive-ROM	Blood flow velocity and vascular resistance in the femoral artery during passive-ROM in a leg	Circulatory variables during an intervention with a bedside cycle ergometer
Study Design	Experimental prospective design	Experimental prospective design	Experimental prospective design	Experimental prospective design
Setting	NICU Sahlgrenska University Hospital Sweden	NICU Sahlgrenska University Hospital Sweden	NICU Sahlgrenska University Hospital Sweden	NICU Sahlgrenska University Hospital Sweden
Participants	11 Patients (4 women)	12 patients (1 woman) 12 Healthy Volunteers (1 woman)		20 Patients (7 women)
Data collection	Circulatory and respiratory variables	Transcranial doppler ultrasound and circulatory variables	Ultrasound and circulatory variables	Circulatory variables
Analyses	Parametric statistical analyses	Non-parametric statistical analyses	Non-parametric statistical analyses	Parametric statistical analyses

ROM - range of motion, NICU - neurointensive care unit

3.1 Patients and Participants

The demographics of the patients in paper I-IV are presented in *Table 4*. In paper II and III we also included a healthy control group matched for age and sex.

Table 4. Demographics of the patients and participants in paper I-IV.

Study	I	II, III	II, III Control group	IV
Number of participants	11	12	12	20
Sex male/female (n)	7/4	11/1	11/1	13/7
Age year	51±11	43±19	44±19	49±18
Mechanical ventilation (n)	11	12		19
Diagnoses (n) SDH		1		
SAH	3			1
CH				1
TBI	6	9		15
ICH	2			2
INF		2		2

Data are presented as mean ± SD or number of patients (n). SDH - subdural haematoma, SAH - subarachnoid haemorrhage, CH - cerebellar haematoma, TBI - traumatic brain injury, ICH - intracerebral haematoma, INF - intracerebral infarction

3.1.1 Paper I

A total of 11 patients were included in this paper between September 2002 and September 2004 from the NICU at Sahlgrenska University Hospital.

Inclusion criteria: age 18 years or more, mechanical ventilation with a minimum fraction of inspired oxygen (FiO₂) of 0.4 and ICP recording via an intraventricular catheter.

Exclusion criteria: fractures making prone position impossible and/or severe heart failure.

3.1.2 Paper II

A total of 12 patients were included in this paper between April and December 2007 from the NICU at Sahlgrenska University Hospital.

Inclusion criteria: age 18 years or more, mechanical ventilation, a parenchymal or intraventricular catheter for ICP measurements and inability to actively move the limbs due to coma and/or sedation.

Exclusion criteria: fractures or other injuries or diseases making passive-ROM impossible.

There were also included a healthy control group matched according to age (± 5 years) and sex in this paper.

3.1.3 Paper III

A total of 12 patients were included in this paper between April and December 2007 from the NICU at Sahlgrenska University Hospital.

Inclusion criteria: age 18 years or more, mechanical ventilation, inability to actively move the limbs due to coma and/or sedation.

Exclusion criteria: fractures or other injuries or diseases making passive-ROM impossible.

There were also included a healthy control group matched according to age (± 5 years) and sex in this paper.

3.1.4 Paper IV

A total of 20 patients were included between August 2013 to July 2014 and November 2014 to February 2015 from the NICU at Sahlgrenska University Hospital. A flowchart of the ICU patients admitted to the NICU during the inclusion period is presented in *Figure 1*.

Inclusion criteria: age 18 year or more, intraventricular or parenchymal catheter for ICP measurements.

Exclusion criteria: subarachnoid haemorrhage, non-Swedish speaking relatives, severe obesity, fractures or other injuries making the intervention impossible.

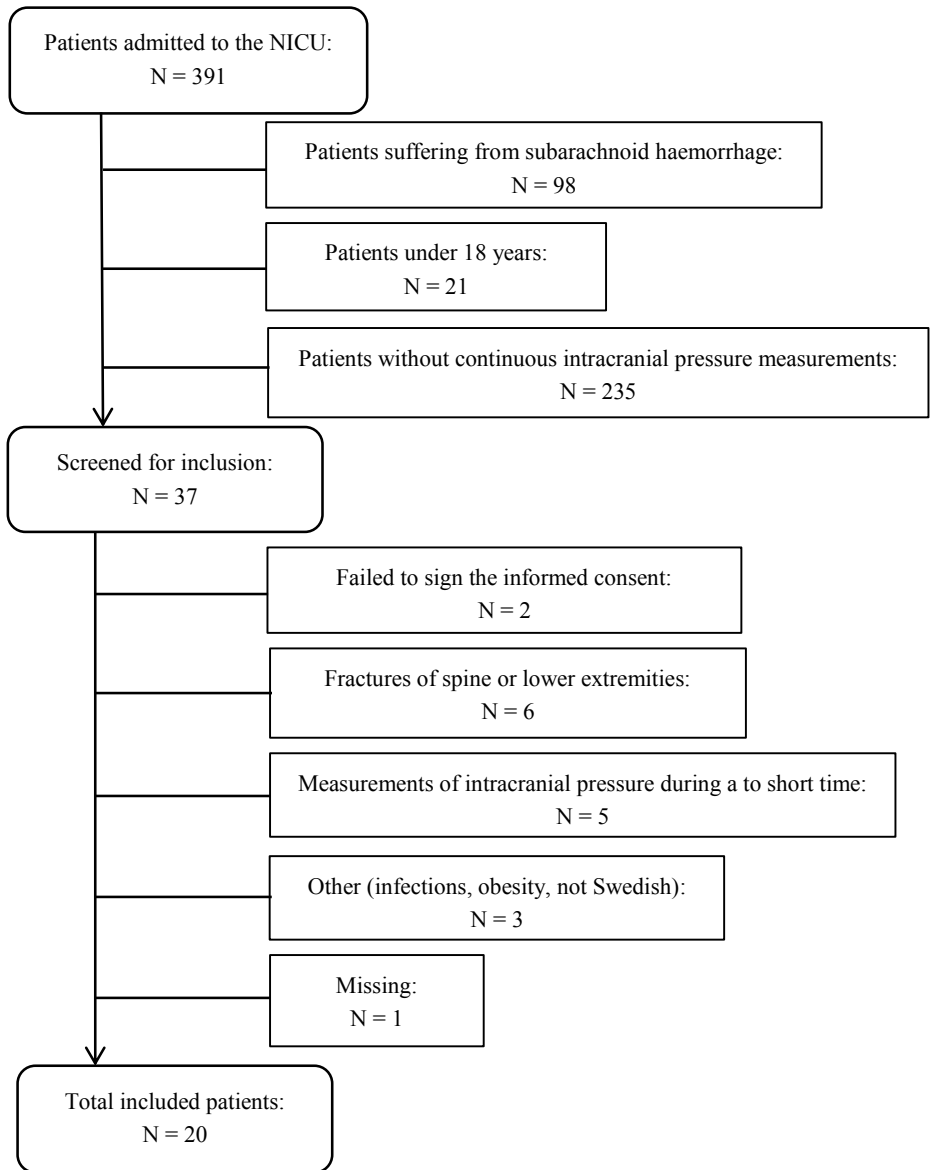


Figure 1. Flow chart over the patients admitted to the neurointensive care unit (NICU).

3.2 Measurements

All the collected data were based on well-established measurement techniques and the acquisition was based on standardized procedures. We therefore did not reevaluate reliability and validity of the obtained measurements in any of the studies. Recorded variables are presented in *Table 5*.

Table 5. Measured variables in study I-IV

Variables	Study I	Study II	Study III	Study IV
ICP/CPP	X	X		X
BP	X	X	X	X
HR	X	X	X	X
SpO ₂				X
PaO ₂ , PaCO ₂ , SaO ₂	X			
Compliance	X			
CBFV/PI		X		
PBFV/RI			X	
CO/SV/SVV				X

ICP - intra cranial pressure, CPP - cerebral perfusion pressure, BP - blood pressure, HR - heart rate, SpO₂ - peripheral oxygen saturation, PaO₂ - arterial partial pressure of oxygen, PaCO₂ - arterial partial pressure of carbon dioxide, SaO₂ - arterial oxygen saturation, Compliance - respiratory system compliance, CBFV - cerebral blood flow velocity, PI - pulsatility index, PBFV - peripheral blood flow velocity, RI - resistance index, CO - cardiac output, SV - stroke volume, SVV - stroke volume variation

In study I, a **Siemens Servo 900E, 300A** (Solna, Sweden) or **Maquets Servoⁱ** (Maquet Nordic AB, Solna Sweden) **ventilator** was used for mechanical ventilation of the patients and in study II-IV the Maquets Servoⁱ was used.

Datex Ohmeda S/5 (Datex-Ohmeda Division Instrumentarium Corp. Helsinki, Finland) was used for measuring and online calculation of ICP, CPP, BP and HR in study I-III and **Philips IntelliVue MX 800** (Philips Healthcare, DA Best, The Netherlands) was used in study IV when obtaining the same variables including SpO₂. In study I, we also used the Datex Ohmeda S/5 to measure the respiratory system compliance. ICP was measured via an intraventricular or parenchymal catheter and CPP were calculated online. BP was obtained from an arterial line in the radial artery,

and HR was monitored by a standard three-lead electrocardiogram (ECG). For the measurements of HR and BP in the control group in study II and III a **Datex cardiocap** (Datex Instrumentarium Corp, Helsinki, Finland) was used. In the control group, HR was measured with a standard three-lead ECG and BP was measured non-invasively.

ABL 700 series (Radiometer A/S, Brønshøj, Denmark) was used for analyzing the blood gases in study I.

For the measurements of blood flow velocity (BFV), PI and RI in study II and III the **PMD 100** (Spencer technologies, Seattle, WA, USA) was used. The middle cerebral artery (MCA) was identified by its topography to the carotid trifurcation and the femoral artery was identified in the groin. BFV, PI and RI were assessed by transcranial Doppler (TCD) software algorithms or manually by cursors in case of weak Doppler signal. PI was measured as $PI = V_s - V_d / V_m$ (i.e. Pulsatility Index = peak systolic blood flow velocity minus end diastolic blood flow velocity divided by mean blood flow velocity). RI was measured as $RI = (V_s - V_d) / V_s$ i.e. (RI= Systolic blood flow velocity minus diastolic blood flow velocity divided by systolic blood flow velocity).

In study IV a **Vigileo Flotrac system** (Edwards Lifesciences, CA, USA) was used for the measurements of cardiac output (CO), SV and stroke volume variance (SVV). This system is minimally invasive and calculates haemodynamic parameters through the arterial line.

To provide the continuous motion during 20 minutes in study IV, a **MOTomed letto** (RECK, Betzenweiler, Germany) was used. The MOTomed letto is an electric bedcycle ergometer that can be used for both passive and active exercise and the user can change back and forth without any interruptions in the exercise. When used for passive exercise it is possible to set the RPM desired and when used for active cycling gears can be set for the optimal exercise effect.

3.3 Procedure

The physiotherapist in charge of the studies screened the ward every day when on duty to evaluate whether any patients met the inclusion criteria. When finding an eligible patient the neurosurgeon-in-charge was asked for consent for study participation. Then the patient's next-of-kin was given both oral and written information about the study and asked for consent to study participation. If the patient's next-of-kin agreed, they signed a written consent form for participation.

In all the studies the intervention was performed only once per patient and no follow-ups were done.

3.3.1 Paper I

The included patients were put into the prone position for three hours before being turned back to the supine position. Before prone positioning, the patients circulatory variables were noted in a study protocol as baseline and a blood gas was taken and analyzed. The same was done during prone position at 10 minutes, 1 hour and 3 hours and then again after the prone position at 10 minutes and at 1 hour. The prone position was achieved by placing the patients in a semi-prone position with their head rotated to one side. If the right side was chosen then the patient's right arm and leg were abducted and flexed, the left leg was straight and the arm was placed straight along the body. The measured circulatory variables were ICP, CPP, mean arterial blood pressure (MAP), and HR and the respiratory variables were arterial partial pressure of oxygen (PaO₂), arterial oxygen saturation (SaO₂), arterial partial pressure of carbon dioxide (PaCO₂) and respiratory system compliance.

3.3.2 Paper II

The included patients underwent one session of passive-ROM lying in the supine position with the backrest of the bed slightly elevated. The passive-ROM movements included the following: flexion/extension of fingers and wrist, pronation/supination and flexion/extension of elbow, flexion/abduction and rotation of the shoulder, flexion/extension of toes and ankle, flexion of the knee and flexion/abduction and rotation of the hip. Every movement was repeated seven times in each joint and in all four extremities of the patient. The study also included one healthy control group matched for age and sex who underwent the same interventions.

Every minute for ten minutes before, during and 10 minutes after the intervention the BP, HR, ICP and CPP were measured. The measurements except for the ICP and CPP were the same for the control group but measured every second minute, and the BP was measured non-invasively in the controls instead of invasively as for the patients. CBFV and PI in the MCA were measured with TCD ultrasound two times before, 2-4 times during the intervention and then twice again at rest.

3.3.3 Paper III

One session of passive-ROM was performed in one leg by a physiotherapist. The movements were flexion/extension of toe and ankle, flexion of the knee and flexion/abduction and rotation of the hip and every movement was repeated seven times per joint and patient. The same movements were also performed in a control group matched for age and sex.

During 10 minutes before, once directly after, and during 10 minutes after the intervention the participants' BP, invasive for the patients and non-invasive for the controls, and HR were measured. The participants' PBFV and RI in the common femoral artery (CFA) were assessed with ultrasound twice before, once directly after and twice at rest after the intervention. Due to difficulties in fixating the ultrasound probe while the participants leg was moving it was impossible to get a reading of the velocity and RI during the intervention, hence this was done directly after the intervention.

3.3.4 Paper IV

The included patients underwent a 20 minute long session of passive leg exercise with a bedside cycle ergometer when lying supine in bed with the backrest of the bed slightly elevated. The cycle was placed at the foot of the bed and the patients feet were fixed in the pedals with soft straps. The cycles pedal rate was preset at 20 RPM for passive cycling and in cases of active cycling the gear was set at zero.

Twice before, three times during and twice after the cycling the patients' circulatory variables including ICP, CPP, BP, HR, CO, SV, SVV and the SpO₂ were measured.

3.4 Statistical analyses

For all statistical analyses the IBM SPSS for Windows (Statistical Package Software System, IBM Corp, NY, USA) was used. For study I, SPSS version 11.0 for study II and III SPSS version 15 and for Study IV, SPSS version 22 was used. Data are presented as means, standard deviations and confidence intervals. P-values used were either $p < 0.05$ or $p < 0.01$ depending on the number of statistical tests.

Statistical tests

For comparison between the measurements in study I and IV a paired samples t-test and in study II and III the Wilcoxon signed-ranks test was used.

In order to analyse the relationship between different variables in study I, a linear regression analysis was used and in study II and III a Mann-Whitney U-test was used when comparing the two groups.

3.5 Ethics

In 1964 the World Medical Association (WMA) developed the Declaration of Helsinki which was amended most recently in 2013. This declaration is a statement of ethical principles for medical research involving human subjects and identifiable human material and data. The Declaration is primarily addressed to physicians but the WMA encourages others who are involved in medical research involving human subjects to adopt these principles as well (131).

All research involving physical interventions on a person or having an aim to influence a person physically or psychologically must be reviewed by an ethical review board. In Sweden there is one Central Ethical Review Board and six regional boards whose task it is to review research applications.

To participate in medical research a written approval prior to the study starting has to be obtained from that individual and after being informed of the following:

- The overall plan for the research
- The aim of the research
- Included methods
- The consequences and risks involved with the research
- The entity principally responsible for the research
- That the participation is voluntary
- That he/she has the right to withdraw his/her participation at any time

When it is impossible to obtain consent for study participation from the person involved in the research it is still allowed if an illness is preventing him/her from being able to be asked, if:

- The result of the research could be of use for the participant or someone else with the same or similar illness or problem
- The research pose an insignificant risk of harm and discomfort for the person

In these cases you have to consult with the person's next-of-kin before the study enrolment (132).

(Translated from: Svensk författningssamling 2003:460)

Oral and written information were given to the patient's next-of-kin, who also gave written consent for study participation. The participants were allowed to withdraw from the study at any point without giving a reason.

Study I was approved by the ethical committee of Sahlgrenska University Hospital, Gothenburg, Sweden.

Study II-IV were approved by the Regional Ethical Review Board of Gothenburg, Sweden.

All studies were conducted according to the Ethical principles of the Declaration of Helsinki.

4 RESULTS

4.1 Main findings

4.1.1 Paper I

Prone position in mechanically ventilated patients with reduced intracranial compliance

One patient had to be turned back to the supine position almost immediately as the ICP rose above 20 mmHg and CPP decreased to less than 60 mmHg. When back in the supine position and after adjustments to sedatives, the patient rapidly recovered. The results are based on the 11 patients that completed the intervention. The main results are presented in *Table 6*.

No changes in ICP were seen between before, during and after the prone position. After 1 hour in the supine post-prone position, CPP and MAP were significantly lower when compared to values measured at 1 and 3 hours during prone positioning. HR was higher during prone and 10 minutes after the prone position compared to baseline.

No changes were seen in PaCO₂ during the intervention. During the prone position the PaO₂ and SaO₂ improved compared to baseline. In the supine post-prone position PaO₂ and respiratory system compliance were higher at 10 minutes and 1 hour respectively, compared to baseline.

It was also noted that patients requiring more oxygen and positive end-expiratory pressure (PEEP) responded to the treatment of prone position with greater improvement in PaO₂ and SaO₂ than those with a lower demand of oxygen and PEEP.

Table 6. Main results from paper I.

	Supine position	Prone position			Supine post-prone position	
	Baseline	10 min	1 hour	3 hours	10 min	1 hour
ICP (mmHg)	16±6	16±5	15±4	16±5	17±6	16±7
CPP (mmHg)	78±12	75±13	78±13	79±10	75±17	72±13†
MAP (mmHg)	94±15	91±13	93±13	95±10	88±17	88±13†
HR (beats/min)	67±15	72±15*	73±15*	76±18*	74±18*	69±14
PaO ₂ (kPa)	13.2±2.1	16.3±6.5	17.3±6.5	19.1±6.1*‡	15.0±2.8*	15.8±4.7
SaO ₂ (%)	97.6±0.8	98.1±0.8	98.4±0.7*	98.6±0.8*‡	98.2±0.8	97.9±1.5
Compliance (ml/cmH ₂ O)	56±18	53±14	52±15	53±19	62±19§	66±23*§

Data are presented as mean ± SD. ICP - intracranial pressure, CPP - cerebral perfusion pressure, MAP - mean arterial blood pressure, HR - heart rate, PaO₂ - arterial partial pressure of oxygen, SaO₂ - arterial oxygen saturation, Compliance - respiratory system compliance

*p<0.05 vs. baseline

†p<0.05 vs. 1 and 3 hours in the prone position

‡p<0.05 vs. 10 min and 1 h in the supine post-prone position

§p<0.05 vs. the prone position

4.1.2 Paper II

Cerebrovascular and systemic haemodynamic parameters during passive exercise

No patients were excluded as per the exclusion criteria set prior to start. The main results are presented in *Table 7*.

CBFV, BP and HR did not differ between the two groups before commencing the passive-ROM. However, there was a significantly higher PI in the patient group vs. the control group.

CPP, BP and HR did not change in the patient group before, during and after the intervention. There was however, a significantly lower ICP after,

compared to during, the intervention. When dividing the patient group into those with high ICP (i.e. ICP>15 mmHg) or low ICP (i.e. ICP<15 mmHg) there were no significant changes in ICP, CPP, BP or HR in either of the two groups during the intervention. In the control group, systolic arterial blood pressure (SAP) and MAP decreased during the intervention and were also lower after the intervention when compared to before passive-ROM.

Passive-ROM did not induce any significant changes in CBFV and PI in either the patient group or the control group. Furthermore, there were no changes in CBFV or PI in the patient group with high ICP (above 15 mmHg).

Table 7. Main results from paper II.

	Patients			Controls		
	Before	During	After	Before	During	After
ICP (mmHg)	15±3	15±3	14±3*			
CPP (mmHg)	76±7	76±7	77±7			
SAP (mmHg)	134±12	134±13	134±14	133±9†	128±8	129±8
MAP (mmHg)	91±7	91±7	90±7	94±7†	91±6	91±6
CBFV/Vm (cm/s)	45±11	45±11	44±12	39±9	40±9	39±9
PI	1.21±0.17	1.23±0.18	1.24±0.19	0.90±0.09‡	0.86±0.07‡	0.86±0.08‡

Data are presented as mean ± 95% CI. ICP - intracranial pressure, CPP - cerebral perfusion pressure, SAP - systolic arterial blood pressure, MAP - mean arterial blood pressure, CBFV/Vm – mean cerebral blood flow velocity, PI - pulsatility index

*p<0.001 vs. during the intervention

†p<0.001 vs. during and after the intervention

‡p<0.001 compared to the patients

4.1.3 Paper III

Blood flow velocity and vascular resistance during passive leg exercise in the critically ill patient

No patients were excluded as per the exclusion criteria. The main results are presented in *Table 8*.

When comparing the two groups there were no significant differences in BP or HR, but the patient group had a significantly higher PBFV and lower RI than the controls.

In the patient group BP, HR, PBFV and RI were not affected by the intervention. In the control group, BP decreased during and after the intervention compared to before, while HR, PBFV and RI remained unchanged.

Table 8. Main results from study III

	Patients			Controls		
	Before	Directly after	After	Before	Directly after	After
SAP (mmHg)	134±19	137±20	134±21	133±15	129±14*	129±13*
MAP (mmHg)	91±10	92±11	90±12	94±12	91±11	91±11*
CFA/Vs (cm/s)	80±27	80±24†	75±20	60±10	55±10	60±8
CFA/Vm (cm/s)	20±12†	21±10†	19±9†	9±3	9±3	7±1
RI	1.28±0.15†	1.28±0.14	1.27±0.17†	1.43±0.06	1.41±0.08	1.48±0.06

Data are presented as mean ± SD. SAP - systolic arterial blood pressure, MAP - mean arterial blood pressure, CFA/Vs - common femoral artery systolic velocity, CFA/Vm - common femoral artery mean velocity, RI - resistance index

*p<0.01 vs before passive-ROM in the controls

†p<0.01 compared to the controls

4.1.4 Paper IV

Effects of early bedside cycle exercise on intracranial pressure and systemic haemodynamics in critically ill patients in a neurointensive care unit.

All 20 included patients completed the intervention without any adverse events. The main results are presented in *Table 9*.

Early exercise with a bedside cycle significantly increased MAP and SV during exercise. After exercise MAP, SV, CO and CPP decreased significantly compared to during exercise. No statistically significant

differences were seen in ICP, HR, SpO₂ or SVV. There were no differences between data obtained after vs. before exercise in any of the recorded variables.

Of the 20 patients included, two patients actively pedalled for about 5 of the 20 minutes, the rest were only passively cycling. We also found that some of the patients that were semi-awake did not have the endurance to cycle for the whole 20 minutes, as they tried to remove their feet from the pedals after about 17 minutes. In one patient with a high leg muscle tone, which made it difficult to place the feet in the pedals, the increased leg muscle tone vanished after 20 minutes of exercise.

Table 9. Main results from study IV.

	Before exercise	During exercise	After exercise
ICP (mmHg)	11±2	12±3	12±3
CPP (mmHg)	83±9	86±8	82±9††
MAP (mmHg)	94±8	97±7*	94±8††
CO (L/min)	6.8±2.1	7.1±2.2	6.8±2.2†
SV (ml/beat)	99±25	105±28**	99±27†

Data are presented as mean ± SD. ICP – intracranial pressure, CPP - cerebral perfusion pressure, MAP - mean arterial blood pressure, CO - cardiac output, SV - stroke volume
 *p<0.05, **p<0.01 during vs. before the intervention
 †p<0.05, ††p<0.01 after vs. during the intervention

5 DISCUSSION

The studies included in this thesis were performed due to a lack of published evidence for the safety of prone position, passive-ROM and CPM when used in patients that are critically ill due to severe brain injury or stroke when treated in a NICU. The studies confirmed and revealed information about haemodynamic and respiratory responses to three different physiotherapy treatments used in the NICU. A short duration of prone position, passive-ROM and bedside cycle ergometry are safe to use in critically ill patients suffering from brain injuries or stroke when admitted to a NICU since the intracranial and haemodynamic responses are small and physiologically harmless. CBFV, PI, PBFV and RI were not affected by passive-ROM exercises and prone position increased oxygenation in this patient group. There were also no changes in CBFV, PI, PBFV, RI or HR during passive-ROM in a healthy control group, but a significantly higher BP was noted before the exercise. However, the patients' haemodynamic reactions should always be closely monitored due to safety reasons when the interventions are used.

5.1 General methodology

No randomized controlled trials (RCT) were used in the studies included in this thesis, even though this is the gold standard for clinical research (133, 134). Since the main goal in the four studies was to investigate the haemodynamic and respiratory responses to three different physiotherapy treatments and the peripheral circulatory effect of a specific treatment, we chose not to do them as RCTs. In studies like these, in order to do them as RCTs the only way is to include a patient group with the same inclusion criteria on whom all the measurements are done but to do these measurements while they are lying still in bed. The patients in the present study were their own control group since physiological variables were measured pre-, during- and post exercise. Including a control group also makes the inclusion period twice as long. There were also a low number of patients who fulfilled the inclusion criteria in Study I-IV. Instead, the decision was made to include a healthy age and sex matched control group in study II and III for comparison. Study I would be the most suitable to perform as a RCT. In hindsight since it took two years to include the patients it would have taken at least four years to complete the inclusion with 12

patients in each group. When this study was performed, prone position was already a highly established treatment at the NICU at Sahlgrenska University Hospital for mechanically ventilated patient with a high oxygen demand. This would have made it very difficult, if not impossible, to persuade the staff not to use prone position in the patients they thought needed it. Studies where you add or retract a treatment and studies where you compare different treatments is the optimal study-design for doing as an RCT. Many studies performed in ICUs are not the optimal studies to do as RCTs and are therefore done as interventional studies without a randomized control group. These studies are often performed very well, revealing new knowledge or confirming old findings but alas do not get the attention they deserve as, they are not RCTs.

Blinding the investigator could have been possible in all four studies if one investigator performed the data collection and another the calculations, but would also have required more personnel. Blinding the patients in studies like this is something that could be debated. To blind a person in studies concerning movements that are as big as they are in these four studies, is a difficult task. A person can feel if he/she is in prone or supine position and if he/she is cycling or not, or if someone is moving his/her arms and legs. Even if the patients are sedated and/or comatose, they would be able to feel if something is happening to them, they may not be able to say exactly what is happening but certainly that something had happened to them.

Study II and III were labelled as cross-sectional studies. There were, however, two options for labelling the studies, cross-sectional or longitudinal. To do a cross-sectional study is to collect data and/or compare groups once, at one point in time and without any follow-ups over time. A longitudinal study is when the studied subjects are followed over time with continuous or repeated measures (135). In the present studies the observations were made during a period of 30 minutes, which would indicate a longitudinal study, albeit one of a short duration. However, the data collection in study II and III was done once and once per person, thus making it a cross-sectional study. Therefore, the decision was to label them as cross-sectional since we think it fits better.

5.2 Statistics

There are two different schools when doing statistics on values like the ones in these 4 studies i.e. parametric and non-parametric statistical tests. The main differences between parametric and non-parametric tests are that parametric tests assume a normal distribution of the measured variables, often have a higher statistical power and are calculated based on the mean. Non-parametric tests do not make assumptions, are less affected by outliers and conclusions are drawn from the ranks (135, 136). In paper I and IV parametric statistical tests were used and in study II and III non-parametric statistical tests were used. When the first study was performed the prevailing statistical method in research was parametric calculations, hence it was used here too. When performing study II and III knowledge had increased both concerning parametric and non-parametric tests. In these studies, there were a few outliers in the patient group and both the patient and the control group were quite small, hence the non-parametric tests were used. In study IV parametric tests were used, however, calculations with non-parametric tests were performed too, to see if they differed. With parametric tests, 6 significant results were noted. With non-parametric tests the same 6 significant results were seen and 2 more significant results were uncovered. In order to reduce the risk for type 1 errors and due to the larger patient group parametric tests were used in study IV.

The generally decided and most commonly used level of significance is 0.05 which means that there is a margin of error at 5%. In paper I and IV a p-value of 0.05 was used, but in paper II and II a p-value of 0.01 was used in order to decrease the risk for type 1 error due to the many statistical tests.

Power calculations were not performed for the inclusion of patients to study I, III and IV, due to the lack of information from earlier studies to use in calculations. Instead, a reasonable amount of patients to answer the main question which was the patient safety for the different treatments, were included. It took 2 years to include the patients in study I and a longer inclusion period could also have increased the number of confounders, making it harder to draw conclusions from the material. For study II however, a power calculation were performed that revealed a need for 18 included patients. An interim analysis performed after 12 included patients, found no differences in all but one variable, hence, the inclusion of new patients was stopped. To include another 6 patients would not be sufficient to detect any significant differences either since the difference in the

calculated results was too small. It also shows the difficulties in doing power calculations when there is a lack of previously published data to perform the power calculations with.

5.3 Generalizability

In medical research there often is a desire to generalize the results from an often small study population to the whole population defined in the study (135). In the present studies, the desire is to generalize the results from these four studies to the whole population of patients that are critically ill due to severe brain injuries or stroke and admitted to an ICU or NICU. To be able to do that, different aspects such as sex, age of the participants, diagnoses of the participants, place where the study was conducted and drop-outs must be considered.

The distribution of males and females, in the present studies, are uneven with more male in all of the studies. When looking at diagnoses, TBI is the most common in every study and in patients with TBI males are overrepresented (137, 138). Thus, the present studies are probably representative of the larger population, looking at the distribution according to sex. Even though males are overrepresented, the intracranial, haemodynamic and respiratory responses to the different passive interventions investigated in the present studies are probably not affected by the sex of the participants. Hence, it should be possible to generalize the results to both men and women.

Only adult patients were included in the present studies, which is an important aspect to take into consideration when treating children that are critically ill due to severe brain injuries or stroke. There was also a low mean age of the patients, mostly the mean age in studies in patients with severe brain injuries or stroke is about 60-65 years (47, 94, 96) and in the present studies it was between 43-51 years. The difference here might also be the overrepresentation of TBI, since patients with TBI are often younger (137, 139).

The patients in study I-IV have a variety of diagnoses i.e. injuries to the brain or stroke, where TBI was the most common. In all, there was 1 patient with a subdural haematoma, 1 with a cerebellar haematoma, 3 with subarachnoid haemorrhage, 4 with infarctions, 4 with intracerebral haematomas and 30 with TBI. When generalizing the results from the present studies, the variety

and the uneven distribution of diagnoses is one aspect worth considering. However, since TBI is an umbrella term, with a variety of different locations for the haemorrhage, it encompasses many of the other diagnoses.

The present studies were conducted in a high income country (Sweden) with tax-funded healthcare and rehabilitation and in a NICU at a University Hospital. This aspect must be considered when generalizing the results to other countries with other health care systems and economic statuses.

In study IV, one patient was missed and two relatives failed to sign the informed consent documentation. These three patients out of 46 probably did not compromise the generalizability. All the included patients finished the tests and no one withdrew their participation.

5.4 Ethics

In order to protect the rights of human research subjects, all clinical research should comply to the Declaration of Helsinki (131) and be approved by an ethics committee. When wanting to include a patient in clinical research, the optimal method is to ask him/her personally for his/her written informed consent for study participation. This is not always possible for many patients that are critically ill and admitted to an ICU. Studies have shown that as few as 2.6% to 8.9% of eligible patients that are critically ill are able to provide their own consent before study participation (140, 141) and only about one third of the patients are able to give a retrospective consent, demonstrating one of the difficulties when performing clinical studies on the critically ill (141). In the four papers included in this thesis, no one was able to give their own informed consent for study participation. Instead, surrogates were asked, i.e. their next-of-kin, if they thought that their critically ill relative would want to participate in the study. If they approved, they were asked to sign a written consent form. Interestingly, no-one declined to participate in the studies. Unfortunately, two relatives in study IV failed to sign due to unforeseen events, even though they gave verbal consent, so those two patients were excluded. One of the possible reasons that no surrogate declined participation for their next-of-kin in the studies could be that the risks involved in the studies were small. Both patients and surrogates are more likely to consent for study participation if the risks involved are small (142). Another reason could be that they found the physiotherapy interventions very important both for their relative and for other persons that

could have great benefit from the results. Also physiotherapy might be associated with something positive and healthy in the treatment provided to patients. The studies are neither invasive, nor are there potentially painful events associated with the interventions, potentially also explaining why no one declined participation.

Studies have shown that there often are discrepancies between patients and surrogates regarding consent for study participation in critical care research. The surrogates tend to both underestimate and overestimate their relatives wish to participate in clinical research (142, 143). There are two important factors to consider when using a surrogates decision when entering a person into a clinical trial and that is the risk of both a false negative and a false positive enrolment. A false negative enrolment happens when a surrogate declines enrolment but the person him/herself would have accepted to participate i.e. he/she would be excluded against his/her own will. A false positive enrolment occurs when a surrogate accepts enrolment but the person him/herself would not i.e. he/she is included against his/her own will. These important factors have raised great controversies and debates as to use of surrogates as decision-makers for the persons not able to decide for themselves (142).

Still, doing clinical research is very important and necessary in order to improve and develop the treatments available for the critically ill, and as a way of getting more and new knowledge of diseases and injuries as well as how to treat them. If research is not allowed in patients that are not able to give their own consent for study participation, then how will it be possible to expand and evolve the knowledge in how to treat the most critically ill and vulnerable patients?

5.5 Specific discussion for paper I-IV

5.5.1 Paper I

This paper concluded that prone position did not influence ICP, CPP, BP or HR but significantly improved PaO₂, SaO₂ and respiratory system compliance. The improvements in respiratory parameters from prone position have been reported in several studies (104, 105, 108, 109, 112, 115).

The influence of prone position on intracranial haemodynamic variables has to our knowledge so far only been reported in three studies (116, 117, 119). There are also a few case reports published confirming its safety (not commented on below) (118, 144). These three studies reported slightly different results regarding the intracranial parameters compared to our study. In the present study, no differences at all were found in ICP while the others found a significant rise in ICP with prone position. Neither were there noted any differences in CPP in the present study as well as in the study by Roth et al. (117). However, Nekludov et al (116) found an increase in CPP and Reinprecht et al (119) found a decrease in CPP. Similarly to Reinprecht et al (119) this study found no differences in BP. However, Nekludov et al (116) reported an increase and Roth et al (117) a decrease in BP with prone position. An increase in HR both during and 10 minutes after the prone position compared to before were also found in the present study. This was not the case in the study by Reinprecht et al (119) who found no changes in HR, while the other two studies did not mention HR at all (116, 117).

The position used in the present study was a semi-prone position for three hours, where the patients were placed with their head rotated to one side, if the right side was chosen then the patients right arm and leg were abducted and flexed, the left leg was straight and the arm was placed along the body. Positions used in the other papers were also semi-prone but for 8 hours (117), prone in a stryker frame for one hour (116), and in an air cushion bed for 14 hours (119). The differences of how the patients were placed and how long they were in the prone position might be two of the reasons why the results differ. Furthermore, in two of the studies, a retrospective approach was used. A third reason could be differences in head reference points for obtaining ICP values. In the present study, the ear tragus was used, the other reference point that could be used is the top of the head. A fourth reason could be differences in the degree of head elevation when treatment variables were recorded. In the present study, the bed was placed in a horizontal position when ICP was measured, both in the supine and the prone position. Studies have shown that head-elevation reduces ICP in patients with injuries to the brain (145, 146), maybe explaining the differences in results between the present study and the other three. Despite the different results, the authors seem to agree that prone position is a treatment that could be used in this patient cohort, since the positive effects on oxygenation exceeds the potential risks of the treatment (116, 117, 119). However, it should be used cautiously and under continuous monitoring of vital parameters.

In the present study, one patient had to be turned back to the supine position almost immediately after turned prone due to a rise in ICP and a decreased CPP. The patient recovered in the supine position after increasing the level of sedation. This patient was excluded from the study. Thus, one in twelve patients i.e. 8 % of the patients in this study did not tolerate the prone position.

Patients are easily placed in a semi-prone position like the one used in the present study and could be done with as few as 3 staff members familiar with the procedure. Since this procedure caused no changes in either ICP or CPP in 11 out of 12 patients it might be a position that could be used more frequently in patients with respiratory problems to lower the inspired fraction of oxygen. One study, written in German, compared the semi-prone position to the prone position according to the effects on oxygenation. According to the abstract both positions resulted in an increase in oxygenation and the incidence of side effects tended to be higher in the prone than semi-prone position (114).

The present study had a prospective, consecutive design meaning that the ward was screened by the physiotherapist every day when on duty, including every patient that met the inclusion criteria on those days.

It took 2 years to include the 11 patients in the study, the reason being that only patients with intraventricular catheters for ICP measurements were included. At the time when the present study started its inclusion period the neurosurgeons started to use more and more parenchymal catheters for ICP measurements and they were not included in the ethics approval. There were also quite a few patients with fascial fractures during the inclusion period. In the NICU at Sahlgrenska University Hospital there is about one patient a month who meets the inclusion criteria for this study, if both intraventricular and parenchymal devices are counted.

In summary, this semi-prone position could be considered to enhance oxygenation in patients that are critically ill and mechanically ventilated due to severe brain injury or stroke.

5.5.2 Paper II

This paper concluded that passive-ROM was safe to use in patients that are critically ill due to brain injury or stroke when admitted to a NICU. Passive-

ROM did not induce any significant changes of the measured haemodynamic variables except for a small decrease in ICP after passive-ROM compared to during.

ICP, CPP, BP and HR

In accordance with other studies the conclusion of the present study was that passive-ROM in this cohort of patients can be considered as a safe and feasible treatment (127-129). The present study found a decrease in ICP after the intervention and no changes in CPP, whereas Roth et al. (129) found a decrease in ICP and an increase in CPP during passive-ROM. Brimiouille et al. (127) found a decrease in ICP and a rise in CPP when the patients were in supine position during passive-ROM with no changes in a 30 and 40 degrees of head up position. There are also differences reported in HR where one report found an increase (127) and one found a decrease (129) while two found no changes at all (128, 147). BP measured as MAP or SAP did not change in the reports. Interestingly Koch et al. (128) found no significant changes in neither ICP, CPP, BP nor HR. From a safety point of view, the changes found in the different reports are very small and not clinically relevant for this group of patients.

In the healthy age and sex matched control group, a significantly higher BP before versus during or after the intervention were found. The conclusion being, this was probably due to the excitement and stress of participating in a study and not knowing exactly what to expect.

CBFV and PI

To our knowledge there has been no previous study on the effect of passive-ROM on CBFV and PI measured in the MCA during passive-ROM in this cohort of patients. The present study found no significant changes when comparing before with during or after passive ROM in either the patient or the control group. Another study however found an increase in CBFV during passive exercise in healthy individuals (148), the differences in results between this and the previous study may be explained by different passive-ROM protocols.

When comparing the results from the patients with the healthy controls' results, a significantly higher PI in the patients was found. The PI value in the controls was around 85-90 which is around the normal range for healthy adults (149) indicating that the patients had a higher PI than healthy individuals. Some studies have shown that PI positively correlates with ICP

(150, 151). Since there were no changes in the haemodynamic variables during the intervention and many of the patients in study II had a raised ICP, due to space occupying lesions and swelling of the brain, it is the most probable reason for the differences observed.

TCD is a non-invasive tool for measuring the cerebral blood flow but its usefulness is debated in the field, with both pros and cons (150, 152-154). The main obstacle when performing TCD is the skull bone, so in order to be able to identify the intracranial vessels you have to place the probe where the skull bone is thinner, an acoustic window. The most commonly used window and the one used in this study is the trans-temporal window. To identify the intracranial vessels, the following elements are used: velocity and direction, depth of signal capture, possibility of following vessels through its whole length, spatial relationship with other vessels and response to lateral and contralateral carotid compression. TCD is mostly used in a NICU to detect for vasospasm, non-invasive estimation of ICP and assessment of brain death (155). All the TCD measurements in this study were performed by a very skilled physician with many years of experience in this measurement, making the results very reliable.

In summary, according to the above results passive-ROM could be performed early in the treatment of patients suffering from severe brain injury or stroke.

5.5.3 Paper III

This paper concluded that passive-ROM of a leg, performed manually by a physiotherapist did not alter PBFV or RI in the CFA.

To our knowledge, there has been no previous study on the effect of passive-ROM on PBFV or RI in CFA in patients that are critically ill and admitted to an ICU or NICU before. The present study found no changes in PBFV or RI, in neither the controls nor the patient group, when exposed to passive-ROM. These findings are supported by Woerds et al (156) who investigated PBFV and vascular resistance in a group of subjects with spinal cord injuries and an uninjured control group. Passive-ROM did not induce changes in BFV or resistance in either of the groups. However, in the present study, a significantly higher PBFV and lower RI were seen in the patient group probably depending on the total relaxation of the patients due to coma and/or sedation.

The lack of effect of passive-ROM on PBFV and RI was somewhat surprising, because as a physiotherapist when performing passive-ROM, you sometimes feel and see the foot of the patient getting warmer and having a better color.

In summary, passive-ROM in a leg does not influence PBFV or RI.

5.5.4 Paper IV

This paper concluded that a longer period of CPM with a bedside cycle ergometer does not yield any significant changes in intracranial or systemic haemodynamic variables between before and after the cycling intervention.

No deleterious effects of the intracranial or systemic haemodynamic variables or adverse events were found during this early bedside cycle exercise and all of the 20 included patients completed the intervention. The use of a bedside cycle ergometer, like the one used in this study, gives the patients longer periods of passive-ROM than the physiotherapist have the strength and stamina to do and is also very easy to perform.

The significant changes of the various variables found in this study were generally small. A significantly higher MAP and SV were found during the intervention. Higher CPP, MAP, CO and SV during versus after the intervention were also noted. The intracranial haemodynamics have to our knowledge not previously been investigated during passive cycling exercise. No significant changes in ICP but a higher CPP during versus after the exercise were found depending on the higher MAP during the intervention. An increase in CPP without any changes in ICP may lead to better perfusion of the brain during exercise. Burtin et al and Pires-Neto et al. when using a bedside cycle for patients in an ICU reported that they generally found no changes or no clinically relevant changes in BP (31, 50). On the other hand Burtin et al. had to terminate prematurely in 6 out of 425 sessions due to a rise in SAP above 180 mmHg (31). The increase in BP in the present study however, was very small and not clinically relevant.

The increase found in CO, during the exercise in the present study, was caused by the increase in SV since the HR was not affected by the intervention. This effect has previously been noted in healthy individuals during passive cycling exercise. During active cycling exercise, on the other hand, an increase in CO could be found due to a rise in HR without any

increases in SV (157). Hence, the rise in CO during passive cycling exercise is most likely caused by an increased venous return from the legs.

When looking at the results in the present study one can see that CPP, MAP, CO and SV values were higher during versus both before and after the intervention. Even though it did not reach statistical significance there was a clear trend for a higher CPP and CO with p-values of 0.057 and 0.066 respectively, during cycling compared to baseline.

The Vigileo Flotrac system is a simple way to measure CO, SV and SVV, without external calibration in patients in a NICU since they almost always have an arterial line inserted for BP measurements. However, in order to get a valid result the patient needs to hold his hand/arm absolutely still to achieve a good and reliable waveform of the arterial line with no artefact. A pulmonary-artery catheter (PAC) is the gold-standard technique to measure CO and SV by thermodilution in the intensive care unit and is frequently used in e.g. cardiac surgery (158). When comparing the absolute CO values from a PAC to those from the Vigileo system however, the agreement is poor in patients during rapid haemodynamic changes and with haemodynamic instability undergoing thoracic or abdominal surgery (159-162). However, in patients that are haemodynamically stable and as a way of detecting trends, the Vigileo system is a reliable tool for CO measurements (163, 164). In the present study, the Vigileo was utilized on patients that are quite young and without any major heart problems. The ongoing intravenous pharmacological and fluid treatments as well as ventilation settings were unchanged during the whole period.

In summary, a bedside cycle ergometer could be used for exercise early in the treatment in patients that are critically ill due to brain injury or stroke since it does not influence the ICP and the haemodynamic responses are small.

5.6 Clinical implications

Findings from this thesis increase the knowledge on intracranial and systemic haemodynamics during three different passive physiotherapy treatments, widely used in ICUs and NICUs all over the world.

Concluded were that physiotherapy interventions in the form of prone position, passive-ROM and CPM with a bedside cycle ergometer could be

started early after the primary injury for patients with severe brain injuries or stroke when admitted to a NICU. Prone position could be used to improve oxygenation in patients with severe brain injuries or stroke when admitted to a NICU.

Suggested are that physiotherapy treatments could be started earlier and with more intensity in this cohort of patients in order to achieve improved physical fitness when leaving the NICU. After a severe brain injury or stroke the patients are often in need of a long rehabilitation period. The stronger the patients are when leaving the NICU, the sooner they should be able to intensify the rehabilitation in order to improve physical fitness and health related quality of life as fast as possible to get back to as good a life as possible and shorten the subsequent hospital stay.

6 CONCLUSION

The following specific conclusions are drawn from paper I-IV:

- Turning critically ill patients in a neurointensive care unit from the supine to the prone position is considered a safe treatment since it did not influence intracranial pressure, cerebral perfusion pressure or blood pressure, but significantly improved arterial partial pressure of oxygen, arterial oxygen saturation and respiratory system compliance.
- Passive range of motion performed by a physiotherapist is considered a safe treatment for patients with severe brain injury or stroke when admitted to a neurointensive care unit. It did not affect cerebral blood flow velocity, pulsatility index, cerebral perfusion pressure, blood pressure or heart rate but significantly reduced intracranial pressure. Neither did it affect cerebral blood flow velocity, pulsatility index, blood pressure or heart rate in a healthy control group.
- Passive range of motion did not alter peripheral blood flow velocity or resistance index in the common femoral artery in patients that are critically ill nor in a healthy control group.
- Early implemented exercise with a bedside cycle ergometer for patients with severe brain injury or stroke, when admitted to a neurointensive care unit, is considered to be a physiologically safe procedure.

In summary: Short durations of prone position, passive range of motion performed by a physiotherapist and continuous passive motion with a bedcycle can be considered as safe treatments in patients that are critically ill due to a brain injury or stroke when treated in a neurointensive care unit. These interventions did not cause any physiologically harmful changes in intracranial, haemodynamic or respiratory parameters.

7 FUTURE PERSPECTIVES

Several questions for future research have arisen during the work on this thesis.

- What is the optimal position for, the optimal duration of and when should a patient be placed in the prone position?
- Could shorter durations of daily semi-prone position, at onset of mechanical ventilation, reduce the incidence of lung problems, shorten the time of mechanical ventilation, reduce NICU and hospital stay and reduce costs in the NICU?
- Is it possible to prevent contractures and to maintain ROM by passive-ROM exercises, and if so, what is the optimal duration and frequency for the intervention and when should it be started?
- Could exercise with a bedside cycle ergometer be used in patients suffering from subarachnoid haemorrhage when restricted to in bed activities?
- Could exercise with a bedside cycle ergometer be used for the patients that are very motor disturbed or have a high leg muscle tone, in order to make the patient calmer and more relaxed?

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