Traumatic Brain Injury

Prehospital challenges and opportunities

Iscander Michael Maissan

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Traumatic Brain Injury
Prehospital challenges and opportunities

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Iscander Michael Maissan

born in Leiden, Netherlands.

Erasmus University Rotterdam

Promotor: Prof. Dr. R.J. Stolker

Other members: Prof. Dr. I.M.J. Matthijssen
Prof. Dr. M.H.J. Verhofstadt
Prof. Dr. A.R. Absalom

Copromotor: Dr. D. den Hartog

Contents

List of abbreviations:

ACRM	American Congress of Rehabilitation Medicine
CA	Cronbach's Alpha
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal fluid
CT	Computed Tomography
E	Young's modulus (chapter 3)
EMS	Emergency medical service
ENT	Ear nose throat
ETI	Endotracheal intubation
ETT	Endotracheal tube
EU	European Union
GCS	Glasgow coma scale
HEMS	Helicopter emergency medical service
ICC	Intraclass correlation coefficient
ICP	Intracranial pressure
ICU	Intensive care unit
LoA	Limits of agreement
MAP	Mean arterial pressure
MDD	Minimal detectable differences
MRI	Magnetic resonance imaging
ONS	Optical nerve sheath
ONSD	Optic nerve sheath diameter
P-HEMS	physician staffed helicopter emergency medical service
POCUS	Point of care ultrasound
R	Distended radius value (chapter 3)
$\mathbf{R_0}$	Distended radius value back to zero (chapter 3)
Rx	Reliability coefficient
ROC	Receiver operating characteristic
SD	Standard deviation
SEM	Standard error of measurement
sTBI	Severe traumatic brain injury
TBI	Traumatic brain injury
TCD	Transcranial Doppler
USA	United states of America
WHO	world Health Organization

CHAPTER 1

General introduction

Definition of traumatic brain injury

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[1] Traditionally it is the leading cause of death in young people in the western world and a disproportionate burden of disability and death in all ages in low and middle income countries.[1]

For decades the term 'head injury' has been used in epidemiological databases throughout the world as the definition of brain injured patients. Besides actual TBI patients, people with for example facial fractures without any damage to the brain or effects on brain function have falsely been included.[2] Nowadays the definition has been replaced by the more exact term 'traumatic brain injury' but still these terms are mixed up in daily statistics leading to unclear data especially at the mild end of the TBI severity spectrum.[3] Also, the definition of altered mental status after a mild brain injury differs between organizations like the WHO task force and the American Congress of Rehabilitation Medicine (ACRM) that monitor the incidence of TBI in a region.[3] ACRM include "any alteration of mental state at the time of accident (dazed, disoriented, or confused)," whereas the WHO Task Force has changed this definition to "confusion and disorientation."[4,5]

Incidence of TBI

Worldwide, approximately 50 million people are involved in an incident leading to TBI each year, and it is estimated that about half the world's population will have one or more of these events leading to TBI's over their lifetime. The estimated costs of TBI worldwide are up to 350 billion euro's annually.[2] Although the incidence of TBI is increasing worldwide, society is unaware to a great extent of this socio-economic and critical health problem. It is therefore referred to as 'the silent epidemic'.[6]

Alarmingly, the incidence of TBI is increasing worldwide. In low and middle income countries this is mainly due to a rise in the number of road traffic incidents, as more people can afford motorized vehicles nowadays.[2] The proportion of TBI due to road traffic accidents has decreased over the last decades in high income countries (due to implementation of speed limits, airbags, seatbelts, helmets and roundabouts), however the overall incidence of TBI is increasing here too.[2]

This recent increase in the **western world** is mainly due to falls of elderly people.[2,7] People in these high income countries have an increased life-expectancy and stay mobile and physically active up to an old age.[3] Patients over 75 years of age often have multiple comorbidities and use more medication like oral anti-coagulants that worsen outcome after TBI.[8]

In population-based studies with broad definitions of TBI the incidence rates for TBI are substantially higher than in studies based on hospital discharge rates.[2]

Although the hospital admission of TBI patients in Europe is up to three times higher than in the United States of America (USA) the mortality of TBI in the European Union (EU) is reported to be lower. Besides varying definitions and methodological differences in research this higher mortality may be caused by the higher incidence of penetrating head injuries caused by firearms in the USA. The mortality of penetrating TBI due to gunshot wounds is 10.5 per 100.000 people per year in the USA and 1.1 per 100.000 people per year in the EU.[2]

The reported incidence of TBI in the EU in retrospective observational studies varies between countries and regions from 47.3 in Spain to 694 in the republic of San Marino in Italy per 100.000 inhabitants annually.[3,8] It is difficult to produce informative comparisons of these presented data, as the studies vary greatly in definition and case ascertainment methods.[8] A cross-sectional analysis of data estimates TBI to be responsible for around 300 hospital admissions and 12 deaths per 100,000 persons per year in Europe.[9]

The overall incidence of TBI in the Netherlands is reported to be 213,6/100.000/year in the period 2010-2012.[10] More recent the incidence of severe TBI (sTBI) in the Netherlands was reported to be 2.7/100.000 in an estimated population of 16,99 million people in 2017. Most of these patients were male (70,8%) with a median age of 46 (24,65) years ranging from 1 to 97 years. 58.4% had been involved in a road traffic incident of which 37,4% were cyclists. Although mandatory helmet use decreased injury severity in other western countries a helmet law isn't implemented in the Netherlands yet. Until then about 21,8% of annually sTBI's in the Netherlands will be due to accidents with cyclists.[2,11] Falls account for 35.4% of sTBI cases in the period from 2015-2017. Less than 2% was caused by violence and assaults of all sTBI's in the Netherlands [11]

Classification of TBI

The severity of TBI is usually classified with the Glasgow Coma Score (GCS) that was first published in 1974 as an attempt to standardize the description of (impaired) consciousness. This score assesses the response in three physical domains. The Eye response (1-4), the Motor response or Muscular response (1-6) and the Verbal response (1-5) to an external stimulus. If no reaction to vocal or painful stimuli is observed, all domains score one point resulting in a GCS of 3. This is the lowest possible score and represents the most severe impairment of consciousness. If the patient looks at the examiner, obeys orders with an adequate motor response and talks in normal coherent sentences the GCS is 15.[12]

Classification	GCS	Prevalence	Mortality
Mild	13-15	70-90%[2,12]	0.1%[13]
Moderate	9-12	±15%[12]	±10%[13]
Severe	3-8	±10%[12]	±40%[2,13]

Pathophysiology of TBI

Primary brain injury is caused by the mechanical impact during the accident. Brain tissue crushes onto the inner side of the skull and may start to swell (brain edema) and bleed.[14] Patients suffering from sTBI are at the highest risk of developing secondary brain injury.[12,14] This swelling and bleeding of the brain will increase the intra cranial pressure (ICP) in an intact skull and compromise cerebral blood flow (CBF).[12]

Direct impact on the brainstem during the mechanical impact of the trauma can result in a temporary respiratory depression or arrest as a result of some sort of 'brainstem concussion'. The heavier the force of impact on the brain stem, the longer the respiratory pause can take resulting in systemic hypoxemia.[15] Hypo-perfusion of the brain and low systemic oxygen saturation of the blood can cause further ischemic damage to the brain known as secondary brain injury.[12,14-16]

General treatment of TBI

Primary brain injury that results from the mechanical impact can't be cured. All treatment is focused on preventing secondary brain injury to expand and compromise brain perfusion. Because the brain lacks the ability of surviving by temporary anaerobic metabolism the brain cells start to die as soon as circulation stops. Even a short systemic desaturation will reduce the chance of survival and increase the risk of severe disability after TBI. Airway management, adequate ventilation and adequate blood pressure control are of the highest priority and should be performed as soon as possible. Cerebral perfusion pressure (CPP) is associated with CBF.[13] CPP can be calculated from the mean arterial pressure (MAP) and the ICP. CPP = MAP – ICP.[15] The gold standard of invasive ICP monitoring in the intensive care unit (ICU) is by installing a pressure probe in the intra cranial cavitum of the patient through a drilled hole in the skull.[17] MAP can be adjusted by vasomotor drugs and ICP can be lowered by sedative drugs, hypertonic intravenous fluids and surgical interventions to stop the bleeding or evacuating hematomas.

Venous drainage from the head can be improved by rising the headrest of the patients bed up to 30 degrees.

Prehospital treatment of TBI

In sTBI, secondary brain injury may start to evolve direct after the incident occurred and needs prompt medical treatment.[12,14,16,17] The prehospital treatment of severe TBI lacks strong scientific evidence and is often opinion based and the effects of treatment on patients outcome are largely unknown.[11]

Prehospital treatment of TBI in the Netherlands

The Netherlands is a densely populated small, well developed country with a well-organized system of prehospital emergency care with highly trained ambulance nurses that can be accompanied by a P-HEMS in complex cases as sTBI.[11]

As in other high income countries the incidence of TBI due to road traffic incidences in the Netherlands has decreased due to preventive measures but has increased due to falls of elderly patients.[3,7] The mean distances to a level 1 trauma center is about 30 km by road. Most TBI patients (87,2%) are transported by ambulances to a level 1 trauma center. The others are transported by helicopter.[11]

In high complex cases like severe TBI, Dutch ambulance-crews can rely on the medical assistance of a physician staffed helicopter emergency medical service (P-HEMS). Specialized medical care can be initiated as soon as possible on-scene or on-route to the level 1 trauma center.

P-HEMS has to make a split-second-decision without any information about the severity of the primary injury and the level of ICP as a result of that. All comatose patients suspected of having TBI or spontaneous intracranial bleeding are treated the same in some sort of "black box" approach with strategies that are assumed to be beneficial.[11] The consensus of P-HEMS operations in the Netherlands on treating severe TBI patients is based on five on size fits all principles:

1. Securing the airway and restore oxygenation and ventilation as soon as possible[14,18,19]
2. Restore or continue "adequate" blood pressure to restore or preserve cerebral blood flow[14]
3. Decrease cerebral oxygen consumption by analgesia and deep sedation[20]
4. Intra venous administration of hypertonic saline to reduce brain edema in case of lateralization in motor response or pupillary reactions to light [14,21]
5. Direct transport to a level 1 trauma center in full immobilization of the head and spine[14]

These strategies aim at preserving what is left of the brain function after primary injury occurred and reducing or even stopping the expansion of secondary brain injury. If these interventions in itself have counterproductive effects on brain perfusion or even aggravate secondary brain injury is unknown. An instrument to measure the ICP would be of great value to evaluate counterproductive effects of interventions. Nevertheless the gold standard of invasive, intra parenchymatous ICP monitoring is not available in prehospital settings.[24]

The optical nerve sheath right behind the eye is in continuum with the dura mater that surrounds the brain and subarachnoid fluid can percolate freely in and out the sheath when ICP changes.[22] The relationship between the rise in ICP and the distention of the sheaths is been suggested to be linear.[23] Several observational studies describe a correlation between distended ONSD's when ICP is increased.[24] This sheath can be visualized with diagnostic tools as MRI, CT or sonography. Dutch HEMS carry ultrasound machines to the scene that can be used for point of care ultrasound (POCUS). If ONSD can be used on-scene to evaluate ICP changing interventions is unknown. After the airway is secured under sedation and relaxation and hypertonic fluids are administered and immobilizing measures are taken the type of transportation has to be chosen. This depends on the distance to the nearest trauma center and the need for medical interventions during transportation. Helicopter transportation may be faster after the patient is installed in the cabin but medical interventions during the flight are challenging due to the small cabin and a limited number of hands on board.

When P-HEMS arrives on-scene most patients are already attached to the monitor of the ambulance and immobilized on their stretcher ready for transportation by road. Reinstalling the patient in a helicopter takes about 10 minutes after the mandatory medical on-scene HEMS care is given. This explains why most patients in the Netherlands are transported by road to the hospital.

Different outcome after TBI between countries

The variance in incidence and outcome of TBI in the EU may probably also be due to differences in definitions and statistic methodologies as mentioned before, but may also be explained by variation in the level of (pre)hospital emergency care.[25] There are differences between healthcare systems per country in the EU. Especially the organization of prehospital emergency care differs highly between countries in de EU from a road based paramedic staffed ambulance system in one country to a physician staffed helicopter emergency medical systems (P-HEMS) with highly trained medical specialists on-scene in another.[25] Some countries are small and highly populated with short term access to a network of trauma centers for all inhabitants. Other countries have sparsely populated rural areas that have just one small hospital that covers a large area.

Long-term outcome after TBI

After surviving a severe TBI, patients often have to live with substantial physical, psychiatric, emotional and cognitive sequelae that disrupt their lives and that of their families.[2] Because of the relatively young age of these survivors, society has to deal with great financial costs because of the loss of productive life years and the duration of supportive care.[6] Even a small improvement on outcome after severe TBI is of great benefit to society and individual patients.[4]

Scope of relevance of this thesis

This thesis focusses on strategies in prehospital care in restoration and continuation of cerebral perfusion pressure and oxygenation after sTBI. The results are relevant to all TBI patients in the acute prehospital setting, as well as all prehospital care providers that will receive practical tools for treatment and insight in possible adverse outcomes of routine procedures.

Aim of this thesis

This thesis aims to study the effect of current prehospital practice in TBI patients on ICP and potential improvements in techniques of airway management, type of medication, immobilization and transportation in favor of brain perfusion.

Objectives and research questions:

I Is a sonographic measurement of the ONSD an adequate noninvasive tool to evaluate ICP changes during routine medical interventions?

II Is there a linear, elastic relationship between ICP and ONSD in all clinical circumstances or do plastic deformation of the ONS due to shear stress in the wall affects the measurements after exposure to high ICP?

III Does intubation under general anesthesia affect ONSD's representing changes in ICP's and can intravenous Lidocaine blunt the potential response?

IV Since intubation increases ICP which provider in prehospital care in the Netherlands should perform ETI in TBI patients?

V What level of experience and exposure is needed in elective circumstances before a novice provider can be considered to be skilled in ETI?

VI Does the application of a rigid cervical collar around the neck after TBI cause venous stasis in the head resulting in a distended ONSD and thereby raised ICP?

VII Does the Trendelenburg position during helicopter transportation in supine position result in a distended ONSD and thereby raised ICP?

VIII Does intracranial pressure rise during an emergency brake of an ambulance transporting a patient in supine, head first position?

IX Is this ultra-sonographic tool to evaluate ICP changes reliable in all circumstances and in all hands ?

I Is a sonographic measurement of the ONSD an adequate noninvasive tool to evaluate ICP changes during routine medical interventions?

In **chapter 2** we will describe an experiment in which we evaluate if registered changes in ICP during medical interventions in the trachea result in simultaneous changes in ONSD.

II Is there a linear, elastic relationship between ICP and ONSD in all clinical circumstances or do plastic deformation of the ONS due to shear stress in the wall affects the measurements after exposure to high pressure?

In chapter 3 we will describe the elastic modulus and threshold for plastic deformation of the ONS based on a post hoc analysis of an ex vivo study of cadaveric ONS and our clinical study as described in chapter 2.

III Does intubation under general anesthesia affect ONSD's representing changes in ICP's and can intravenous Lidocaine blunt this potential response?

In **chapter 4** we describe the effect of endotracheal intubation and a persistent tube position between the vocal chords on ONSD and thereby ICP in sedated patients. We will administer I.V. Lidocaine prior to intubation in half of the study population and evaluate the effect on ONSD response.

IV Since intubation increases ICP, which provider in prehospital care in the Netherlands should perform ETI in TBI patients?

In **chapter 5** we compare the first-pass, the overall-success rates and the rate of unrecognized esophageal intubations in three provider groups with different experience and exposure.

V What level of experience and exposure is needed in elective circumstances before a novice provider can be considered to be skilled in ETI?

The number of needed intubation to reach a certain level of success in this procedure is described in **chapter 6** of this thesis.

VI Does the application of a rigid cervical collar around the neck after TBI cause venous stasis in the head resulting in a distended ONSD and thereby raised ICP?

In **chapter 7** we describe the effect of the application of a rigid cervical collar on the ONSD in healthy volunteers.

VII Does the Trendelenburg position during helicopter transportation in supine position result in a distended ONSD and thereby raised ICP?

In **chapter 8** we describe the effect of the head down position during helicopter transportation on the ONSD and possible solutions for venous stasis during the flight.

VIII Does intracranial pressure rise during an emergency brake of an ambulance transporting a patient in supine, head first position?

In **chapter 9** we describe the effect of emergency braking on the ONSD in people in supine position in an ambulance and what measures can be taken to diminish this effect.

IX Is this ultra-sonographic tool to evaluate ICP changes reliable in all circumstances and in all hands ?

In **chapter 10** we will describe the results of a systematic review of the literature on intra and inter observer variability of sonographic measurements of the ONSD.

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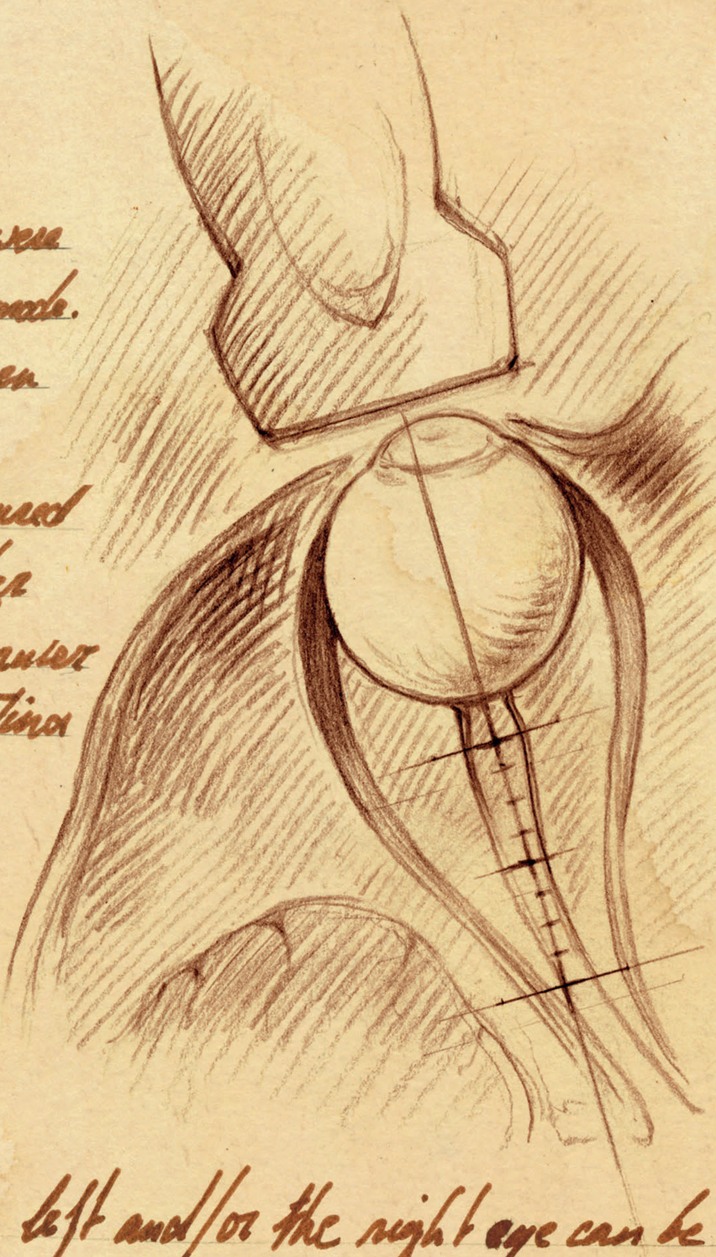
Axial measurements were carried out in B-mode. The images were frozen at the same time. ONSD's were measured by each sonographer with the internal ruler 3mm behind the retina



Images of the left and/or the right eye can be taken with a M-turbo Sonosite Inc. ultrasound machine ([illegible] MHz linear probe; ocular setting, mechanical index = 0.2: FUJIFILM Sonosite Inc., Bothell, WA, USA.)

CHAPTER 2

Ultrasonographic measured optical nerve sheath diameter is an accurate and quick monitor for changes in intracranial pressure

JNS 2015;123:743-47.

Iscander M. Maissan, Perjan J. A. C. Dirven, Iain K. Haitsma,
Diederik Gommers, and Robert Jan Stolker.

Abstract

Backgrounds and aims: Ultrasonographic measurement of the optical nerve sheath diameter (ONSD) is known to be an accurate monitor of elevated intra cranial pressure (ICP). However, it is yet unknown whether fluctuations in ICP result in direct changes in ONSD. Therefore, we researched if ONSD and ICP simultaneously change during ICP by altering tracheal manipulation in traumatic brain injured patients at the intensive care unit.

Materials and methods: We included 18 ICP monitored, traumatic brain injured patients admitted to the intensive care unit. We examined the optical nerve sheath by ultrasound before, during and after tracheal manipulation which is known to increase ICP. The correlation between ONSD and ICP measurements was determined and the diagnostic performance of ONSD measurement was tested using ROC analysis.

Results: In all patients ICP increased during manipulation of the trachea above 20 mmHg and this was directly associated with a dilatation of the ONSD of >5,0 mm. After tracheal manipulation stopped, ICP as well as ONSD decreased immediately to baseline levels. The correlation between ICP and ONSD was high (R^2= 0.80) and at a cut-off of ≥ 5.0 mm ONSD, a sensitivity of 94%, a specificity of 98% and an AUC of 0.99 (95% CI: 0.97-1.00) for detecting elevated ICP was determined.

Conclusions: In patients with traumatic brain injury ultrasonography of the ONSD is an accurate, simple and rapid measurement, for detecting elevated ICP as well as immediate changes in ICP. Therefore, it might be a useful tool to monitor ICP, especially in conditions in which invasive ICP monitoring is not available, such as at trauma scenes.

Introduction

Elevated intracranial pressure (ICP) > 20mmHg is associated with poor outcome after traumatic brain injury (TBI)[2,13]. Especially in the early posttraumatic period, elevated ICP is associated with a high risk of secondary ischemic brain damage. Interventions which lower the ICP should be started as soon as possible in order to optimize cerebral perfusion pressure (CPP) and save brain tissue.[3] Early diagnosis of elevated ICP is therefore essential in preventing this secondary damage. Elevated ICP and disorders in emergency CT scan of the brain have a poor correlation.[12] Invasive intracranial pressure measurement with an intraparenchymal probe is considered to be the golden standard. For safe insertion of the probe, optimal blood coagulation, sterile conditions and a neurosurgeon are required.[6] These are not readily available at the trauma scene. Therefore, a non-invasive, simple bedside method can be beneficial in early detection of increased ICP, especially in the prehospital and emergency care setting.

Transcranial Doppler (TCD) pulsatility index and trans-ocular ultrasonography has been suggested for rapid assessment of elevated ICP. The TCD pulsatility index detects decreases in cerebral perfusion pressure due to an increased ICP[7]. However, TCD is difficult to perform even if experienced.[1,15]

Trans-ocular ultrasonography has been used to detect elevated ICP and has been shown to be accurate.[9,14,15] All previous studies on the relation between ICP and ONSD were performed crossectionally.[9-19] ONSD distension was correlated to the ICP measured at the same moment. However, it remains unclear whether these changes in ONSD resulted only from ICP changes or from papilledema as well. A retrospective study by Rajajee suggests a delayed reversal of nerve sheath distension after ICP fluctuations possibly due to papilledema. This might compromise the specificity of ONSD.[15,17]

Therefore, in this study, we performed dynamic measurements in patients with traumatic brain injury to examine whether ICP change and not papilledema causes changes in ONSD.

Changes in ONSD are directly caused by ICP changes and are not influenced by papilledema.

Materials and Methods

Study design

This observational study was based on a single center prospective research. The Erasmus university medical centre is the biggest trauma center of the South West of the Netherlands.

Patients were included between January 2011 and December 2011 after admission to the intensive care unit of our hospital. All patients had suffered traumatic brain injury, and have had an intraparenchymal probe inserted to monitor ICP. Eligible subjects were at least 18 years old and at least one eye and the orbita should be intact.

Informed consent was given by the patients' representatives. The medical ethical committee of the Erasmus Medical Center Rotterdam approved our study. (MEC-2011-433)

ONSD and invasive ICP measurement protocol

The treatment protocol of increased ICP at the intensive care unit consist of deep sedation, mechanical ventilation and if necessary, frequent infusion of mannitol. This regime is aimed to lower ICP, ideally below 20 mmHg in order to optimize cerebral perfusion.

During routine nursing procedures ICP may rise transiently by manipulation. Especially during suctioning of the endotracheal tube to evacuate sputum, ICP rises rapidly due to irritation of the trachea. Sonography of the ONSD was performed and ICP measurements were recorded simultaneously before, during and after this routine procedure.

The first, baseline measurement was recorded 30-60 seconds prior to cleaning the tube. The second measurement was during suctioning and the third measurement was performed 30-60 seconds after the procedure and all stimulation had stopped.

ONSD was measured at both eyes consecutively, starting with the left eye, except for patients with unilateral eye lacerations. In those three patients only the intact eye was studied. We applied antiseptic ultrasound cream on the closed eyelid and placed a linear probe (7,5Mhz) in the cream just above the eyelid. We freezed the images of the optical nerve sheath with the Micromax ultrasound machine (Sonosite inc. Washington, USA). An integrated ruler was used for measuring the ONSD. The cut-off value for ONSD was $\geq$ 5.0 mm representing ICP > 20 mmHg.

The ICP measurement was recorded by an assisting nurse at the same time the ONS image was frozen on the ultrasound machine. The examiner performing the ONSD measurement was blinded for the ICP monitor. (Pressio monitor system; catheter by Sophysa, Orsay, France) Cut-off for ONSD, for detection of ICP > 20 mmHg, was $\geq$ 5.0 mm. (sensitivity of 94% a specificity 98%).

Statistical analysis

Data were analysed using SPSS 20 (IBM Chicago IL, USA). First, the correlation coefficient between ICP measurement and ONSD was determined. To evaluate the diagnostic performance of the ONSD measurement compared to the golden standard, intraparenchymal ICP measurement, ROC analysis was used.

Number of included subjects	18
Age, mean years (SD)	38 (17)
Male gender, n (%)	12 (67%)
Both eyes measured for ONSD	15 (83%)
One eye measured for ONSD	3 (17%)
Baseline ICP, mean mmHg (SD)	18.2 (5.3)

Table 1. Patient characteristics

Results

In total 18 patients were included. Patient characteristics are shown in table 1 and 2. Twelve patients were male. The mean age was 38 years. All patients were being treated for a proven high ICP by deep sedation, mechanical ventilation and intermitted Mannitol bolus infusions.

As shown in figure 1, as expected, ICP increased during tracheal stimulation and after the procedure rapidly decreased to baseline levels. The diameter of the ocular nerve sheath increased simultaneously with an increased ICP and decreased back to the baseline diameter in the same rate as the ICP (figure 2).

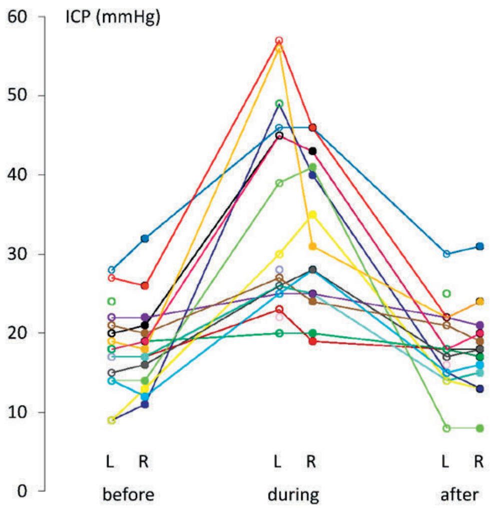


Figure 1. ICP in mmHg of the ○ left and ● right eye before, during and after intervention. Colours correspond to the ONSD data of the same patient in figure 2

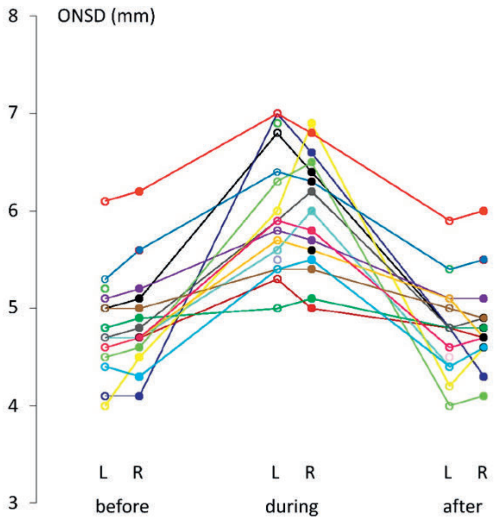


Figure 2. ONSD in mm in the ○ left and ● right eye before during and after intervention. Colours correspond to the ICP data of the same patient in figure 1

We used unique colours for each of the plots to describe each patient.

The correlation between the ICP measurement and the ONSD measurement showed an R^2 of 0.80.(r = 0,895)

The optimal cut-off for ONSD, for detection of ICP > 20 mmHg, was ≥ 5.0 mm with a sensitivity of 94% a specificity 98% and an Area Under the Curve of 0.99 (95% CI: 0.97-1.00).

With this cut-off value of ≥ 5.0 mm ONSD, only one false negative measurement was detected. In this subject, ICP was 20 mmHg while the ONSD measured only 4,7 mm. No false positive measurements were observed.

No.		Age	initial GCS	Mechanism of injury	CT findings	Inclusion
1	male	30	E3M1V1	Road Traffic Collision	Subdural hematoma	one day later
2	female	24	E1M4V1	Fall from Height	Subdural hematoma	3 days later
3	male	52	E1M4V1	Fall from Height	Brain contusions, subarachnoid bleeding	1 day later
4	male	24	E1M2V1	Road Traffic Collision	Epidural and subdural hematoma skull fractures	3 days later
5	male	25	E1M5V1	Direct Blunt trauma to the head	Epidural hematoma, subarachnoid bleeding, skull fractures	1 day later
6	female	71	E1M2V1	Fall from Stairs	Subdural hematoma, subarachnoid bleeding, skull fractures	1 day later
7	male	32	E1M5V1	Road Traffic Collision	Brain contusions, subarachnoid bleeding	same day
8	male	26	E1M1V1	Road Traffic Collision	Subdural hematoma	1 day later
9	male	33	E1M1V1	Fall from Height	Diffuse axonal injury, brain contusion, blood in ventrikels	same day
10	male	60	E1M3V1	Direct Blunt trauma to the head	Epidural hematoma, diffuse swelling of the brain, skull fractures	same day
11	male	31	E1M1V1	Road Traffic Collision	Intra cerebral and subarachnoid bleeding facial fracures	2 days later
12	female	62	E1M2V1	Road Traffic Collision	Subdural hematoma, diffuse axonal injury	same day
13	female	20	E1M5V1	Road Traffic Collision	Subarachnoid bleeding	2 days later
14	female	64	E4M4V1	Fall from stairs	Epidural subdural hematoma, subarachnoid bleeding facial fractures	2 days later
15	male	39	E1M5V1	Unknown	Brain contusions, diffuse swelling of the brain	1 day later
16	female	22	E1M2V1	Road Traffic Collision	Brain contusions, subarachnoid bleeding	same day
17	male	55	E1M1V1	Fall from Height	Subdural hematoma	same day
18	male	33	E1M1V1	Road Traffic Collision	Intra cerebral hematoma	1 day later

Table 2. Patient characteristics

Discussion

In our study, we demonstrate that ultrasonographic ONSD measurement is highly correlated with direct ICP changes. Furthermore, ONSD reflects immediate changes in ICP in patients with traumatic brain injury. An ONSD of 5,0 mm or more predicts an elevated ICP (>20mmHg) with an AUC of 0.99.

The correlation between ONSD and direct measurements of ICP has been studied in adults and children in multiple clinical trials.[4,7,8,10,14,15,19] The cut-off point has been discussed for a number of years. Our results show an optimal cut-off value of 5.0 mm for ONSD in mechanically ventilated patients with traumatic brain injury at the intensive care unit. This is consistent with a previous report.[9]

All previous studies on ONSD measurement as a diagnostic tool for elevated ICP were crossectional in design.[4,7,8,10,14,15,19] In these studies, an increased ONSD was associated with the ICP at the same time. Whether this was a result of immediate ICP changes or due to papilledema has not been studied so far. The underlying mechanism of papilledema is assumed to be similar to ONSD distention, but oedema takes hours or even days to develop in patients with high ICP.[8] This is demonstrated by the retrospective study of Rajejee et al. in which a delayed reversal of ONSD after ICP fluctuations was shown.[17] However, in our study, changes in ICP were reflected by immediate changes in ONSD. In all cases ONSD reverted to baseline levels simultaneous with a decrease of ICP, directly after tracheal manipulation was stopped. Changes in ICP are accurately reflected by changes in ONSD at the same day or several days after trauma.

ONSD measurement with ultrasonography has a reproducibility with a median intra-observer reliability of 0,2mm (0,1 - 0,5mm).[9] Examiners with ultrasonographic experience have an estimated learning curve of as few as 10 subjects with 3 abnormal scan results. For physicians with no experience the needed number of scans is close to 25.[19] Although the learning curve is steep this technique should not be used in non-specialized units by untrained physicians.[14,16,19]

Conditions which could influence the ONSD measurement and might alter the tests specificity include Graves' disease, sarcoidosis, inflammation and tumors. Bilateral ocular trauma can make it impossible to perform ONSD measurement, but this is uncommon in head trauma patients.[17]

In ICU settings, invasive, continuous ICP measurement with the intra cranial pressure probe remains superior to this non-invasive, intermittent ONSD ultrasonography because it delivers continuous values and requires no additional skills from the attending ICU nurse. However, in emergency care and pre hospital conditions ONSD measurement may be useful to distinguish between normal or elevated ICP in comatose patients.[16,17]

If insertion of a probe is contra-indicated in case of infection, or if correct function of the probe is questioned, ONSD sonography might be an alternative.

At low levels ICP (8-10 mmHg) changes do not affect the ONSD. When ICP rises, a linear correlation is seen between ONSD and ICP. The optical nerve sheath (ONS) can distend more than 50% if ICP rises.[19] The sheath's pressure response depends on its elasticity. The elasticity is not uniform among individuals.[10] For this reason measurement of the ONSD is a qualitative rather than quantitative assessment of ICP.[18]

The inter-observer variation is low and measurements are reproducible. However a lot of variables and artefacts might alter the ultrasound findings. Because of acoustic shadows cast by the lamina cribrosa the ONSD might be overestimated.[5] Off-axis measurements result in erroneous values. To minimise these variables and artefacts a standardised technique should be used.[5,18]

Because of the small sample size and the single centre design of this study we might have selected more serious injured patients. Because of the single observer strategy we weren't able to examine the suggested inter-observer variability that was described by Dubourg.[9]

We observed a direct correlation between ICP changes and changes in ONSD. We could not reproduce the suggested effect of delayed return to baseline ONSD by Rajanjee.[18] We did not perform ophthalmic exams to determine the presence of papilledema. Whether or not papilledema was present, it did not influence the correlation between ICP and ONSD changes. Not on the day of trauma nor several days later. We performed two measurements on each patient. One of the left and one of the right eye. We did not have any follow-up in our strategy to find changes in correlation in time in the same patient.

Conclusion

We demonstrated that ultrasonography of the ONSD may be considered as an accurate, simple and rapid measurement not only to detect increased ICP but also immediate changes in ICP in patients with traumatic brain injury. ONSD changes reflect changes in ICP and are not influenced by edema.

It's easy to learn and useful in conditions in which invasive ICP monitoring is not available, such as at trauma scenes.

Our data support results from previous studies that ONSD ≥ 5,0 mm is the optimal cut-off value for detecting elevated ICP (> 20 mmHg).

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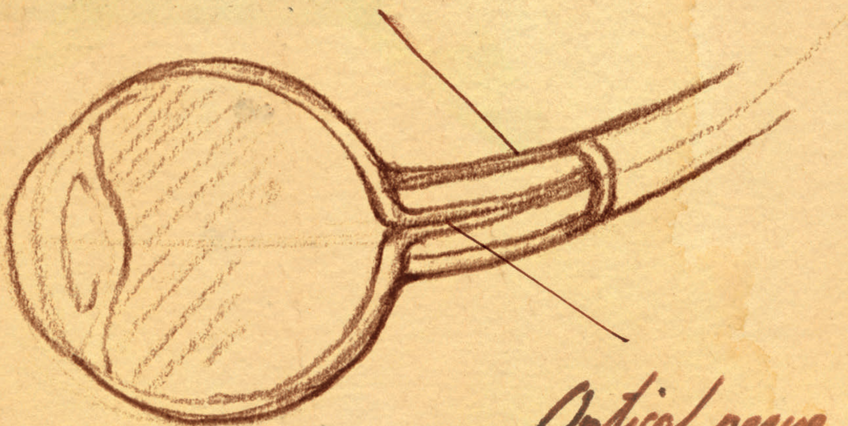
The optical nerve sheath is in continuity with the dura mater. Changes in intra cranial pressure will be reflected by distention of the tissue.



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CHAPTER 3

Optic Nerve Sheath Viscoelastic Properties: Re-Examination of Biomechanical Behavior and Clinical Implications.

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Matthew Luchette, Knut Helmke, Iscander M. Maissan, Hans-Christian Hansen, Robert Jan Stolker, Robert C. Tasker, Alireza Akhondi-Asl.

Abstract

Background: Meta-analyses show a variable relationship between optic nerve sheath diameter (ONSD) and the presence of raised intracranial pressure (ICP). Because optic nerve sheath (ONS) tissue can be deformed, it is possible that ONSD reflects not only the current ICP but also prior deforming biomechanical exposures. In this post hoc analysis of two published data sets, we characterize ONS Young's modulus (E, mechanical stress per unit of strain) and calculate threshold pressure for plastic deformation.

Methods: The authors of two previously published articles contributed primary data for these unique post hoc analyses. Human cadaveric ex vivo measurements of ONSD (n=10) and luminal distending pressure (range 5 to 65 mm Hg) were used to calculate E and the threshold pressure for plastic deformation. Clinical in vivo measurements of ONSD and ICP during endotracheal tube suction from patients with traumatic brain injury (n=15) were used to validate the ex vivo cadaveric findings.

Results: Ex vivo ONS estimate of E was 140±1.3 mm Hg (mean±standard error), with evidence of plastic deformation occurring with distending pressure at 45 mm Hg. Similar E (71±10 mm Hg) was estimated in vivo with an average ICP of 34±2 mm Hg.

Conclusions: Ex vivo, ONS plastic deformation occurs at levels of pressure commonly seen in patients with raised ICP, leading to distortion of the ICP–ONSD relationship. This evidence of plastic deformation may illustrate why meta-analyses fail to identify a single threshold in ONSD associated with the presence of raised ICP. Future studies characterizing time-dependent viscous characteristics of the ONS will help determine the time course of ONS tissue biomechanical behavior.

Introduction

The optic nerve sheath (ONS) is in continuity with the dura mater, and, in theory, change in intracranial pressure (ICP) should be reflected by distension of the tissue. This phenomenon is exploited by the noninvasive measurement of ONS diameter (ONSD) to help identify the presence of raised ICP. However, there remains heterogeneity in the best threshold value of ONSD associated with the presence of raised ICP. In adult studies, for example, the optimal ONSD for determining elevated ICP has ranged from 4.8 to 6.4 mm.[1–3]

The underlying assumption to ONSD measurement is a linear pressure–diameter relationship in the tissue. In biomechanics, the correlation coefficient between a given stress (in this case pressure) and strain (a dimensionless value used to calculate the change in a material's size along a given dimension) is referred to as the Young's modulus (E). The stiffer a material is, that is, the more stress required to create a given strain, the higher the Young's modulus will be.

Although such a linear relationship may be correct for small ICP changes, biomechanical properties of the tissue should also be considered for larger changes.[4–6] In particular, such experiments do not take into account plastic deformation, or irreversible changes to a biological tissue caused by high stresses, which may be seen in patients experiencing elevated ICP.

In this report, we describe a unique biomechanical analysis of ONS tissue using measurements made in

ex vivo human cadaveric tissue and measurements made in patients with traumatic brain injury (TBI).[7,8]

Our primary aim was to characterize the plastic deformation threshold of the ONS using an ex vivo sample. Our secondary aims were to define the Young's modulus of the tissue and to validate our biomechanical measurements with a clinical data set.

Methods

Data Sources

We performed a post hoc biomechanical analysis of two previously published studies: an ex vivo study of

cadaveric ONS and a clinical study in which ONSD was measured in patients with invasive ICP monitors. We contacted the authors of the two reports and asked them to collaborate in this analysis. Both groups of investigators agreed and have contributed to the authorship of this article. Because this was a post hoc analysis of previously published data, the authors did not seek ethical committee approval.

The ex vivo data set comprised ten cadaveric ONS specimens (18–80 years of age) from humans who had died of nonneurological causes.[7] The specimens were submerged at a depth of 5.5 cm in a water tank and deformed with intraluminal hydrostatic pressures ranging from 5 to 65 mm Hg in increments of 10 mm Hg. The ONS then remained at the distending pressure for 200 s before the ONSD was recorded with a 10-MHz ultrasound probe. The ONS intraluminal pressure was then relaxed back to zero pressure before being raised with a subsequent distending pressure.

The in vivo data set was derived from an observational study of 18 adult patients with severe TBI (aged

38±17 years) who had an intraparenchymal ICP transducer in situ.[8] ONSD measurements and brain tissue intraparenchymal ICP were recorded before, during, and after endotracheal tube (ETT) suction. Tree patients from this cohort who did not have identifiable ICP and ONSD measurements before, during, and after ETT suction were excluded.

Biomechanical Calculations

To calculate E of ONS tissue, the ex vivo data were first normalized by calculating the biomechanical strain for each ONSD measurement (Fig. 1, Eq. 1). Then to account for plastic deformation caused by higher distending pressures, we revised the strain calculation using two values for the ONS radius: the distended radius value (R), and the value after decreasing distending pressure back to zero (Ro). We solve for E using a least-squares approach (Fig. 1, Eqs. 2–4). Also, by assuming that E is the same for all tissue specimens, the variance between specimens is then related to noise; the estimate of E is a function of biomechanical stress, whereby increased stress increases estimated tissue stiffness (Fig. 1, Eqs. 5–7).

The threshold pressure, ex vivo, at which plastic deformation occurs was estimated by calculating E for each sample with two different calculations of strain. One calculation used a value for Ro as that measured at the time of initial zero pressure before any distension of the ONS was performed. The other calculation used a value for Ro as that measured at the time ONS distending pressure was returned to baseline zero pressure after the experimental perturbation. If plastic deformation does not occur, the two calculations should be the same. If plastic deformation does occur, however, E calculated using the second value of Ro would be greater than the other estimate. We used analysis of variance, followed by pairwise t-test (corrected with Tukey's honestly significant difference), to determine at which distending pressure plastic deformation was likely to occur. Python 3, MATLAB (R2019b, Natick, Massachusetts), and R-studio (Version 1.3.959) were used for the statistical analyses in this study. All results are presented as mean ± standard error measurement.

Equation 1: Strain	$\varepsilon = \frac{R - R_o}{R_o}$
Equation 2: Least squares calculation	$E = arg\ min_{\mathrm{E}}(\sigma - \varepsilon E)^T(\sigma - \varepsilon E)$
Equation 3: Single point approach	$\epsilon_{70x1}\mathrm{E}_{1x1} = \sigma_{70x1}$
Equation 4: Single point solution	$\epsilon E = \sigma \rightarrow \hat{\mathrm{E}} = (\epsilon^T\epsilon)^{-1}\epsilon^T\sigma = \frac{\epsilon^T\sigma}{\epsilon^T\epsilon}$
Equation 5: Least squares variance	$Var(\hat{\mathrm{E}}) = \frac{1}{k-1}(\epsilon^T\epsilon)^{-1}(\sigma - \hat{\sigma})^T(\sigma - \hat{\sigma})$ where $\hat{\sigma} = \epsilon(\epsilon^T\epsilon)^{-1}\epsilon^T\sigma = \frac{\epsilon\epsilon^T\sigma}{\epsilon^T\epsilon}$ and k = number of samples
Equation 6: Young's modulus with variance of noise $V(\epsilon)$	$\hat{E} = \frac{\sigma\Sigma_i\epsilon_i}{\Sigma_i\epsilon_i^2} = \frac{\frac{\sigma\Sigma_i\epsilon_i}{n}}{\frac{\Sigma_i\epsilon_i^2}{n}} \approx \frac{\sigma E(\epsilon)}{E(\epsilon^2)} = \frac{\sigma E(\epsilon)}{E(\epsilon)^2 + V(\epsilon)}$
Equation 7: Young's modulus with variance, assuming $E(\epsilon) = \frac{\sigma}{E}$ and $V(\epsilon) = \gamma^2$	$\hat{E} \approx \frac{\sigma^2/E}{(\sigma/E)^2 + \gamma^2} = \frac{E}{1 + \frac{E^2\gamma^2}{\sigma^2}}$

Fig. 1 Equations for calculation of Young's modulus (E) and variance of noise. ε strain, R diameter of optic nerve sheath, σ stress, γ2 variance of strain In the in vivo data set, the average peak ICP during ETT suction was 34±2 mm Hg, with an average E of 71±10 mm Hg. A two-sample t-test comparing E calculated with pre- and postdistension ONSD did not show the significance for pressure distensions>40 mm Hg (p=0.85).

We calculated E in the clinical data set using changes in ICP and ONSD measurements before, during, and after ETT suction. R was set to the ONSD when peak ICP was reached. Using a two-sample t-test, the calculated E when Ro was set to the predistension ONSD was compared with the calculated E when Ro was set to the postdistension ONSD for each pressure.

Results

Analysis of the ex vivo ONSD data yielded a value for E of 140±1.3 mm Hg (mean ± standard error). To further characterize changes in E, we calculated its value at each strain ranging from 5 to 65 mm Hg (Fig. 2a).

There is an increase in E at higher distending pressures, which suggests that the elastic properties of ONS tissue change at each strain. Our modeling of measurement noise (Fig. 1, Eq. 7) suggests that when stress is not large enough, as compared with noise, the estimate of E is unreliable. Hence, at lower stress, changes in E (Fig. 2a, range 5–35 mm Hg) are unlikely to be due to changes in the physical properties of ONS tissue but instead due to inherent measurement noise.

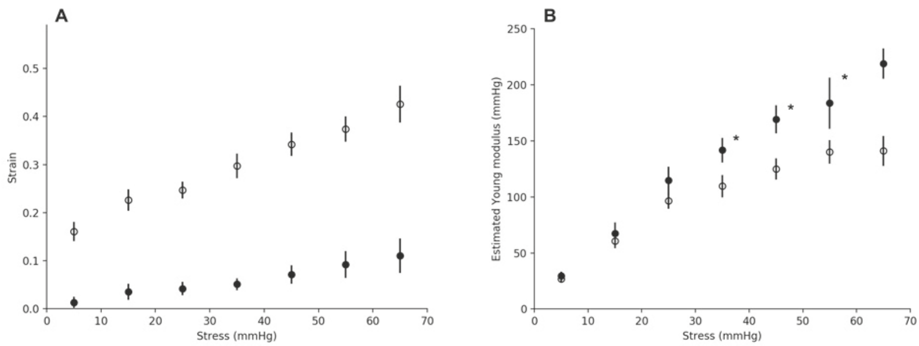

Figure 2a. Elastic and plastic deformation. The Young's modulus (E) was calculated as the ratio of the change in stress to the change in strain. Plastic deformation caused by high-pressure deformation would result in a subsequent baseline diameter that is larger than the predistension baseline diameter. The slope of the stress–strain curve for the ex vivo data (white circles) is E. The increasing baseline optic nerve sheath diameter in the experiment is a result of plastic deformation (black circles).
Figure 2b. Young's modulus (E) and plastic deformation analysis ex vivo. E analyzed from ex vivo data using two calculations of strain: the diameter before distension as the baseline diameter (white circle) and the diameter after distension as the baseline diameter (black circle), with asterisks indicating $p<0.05$

To calculate the ex vivo strain at which plastic deformation occurs, we performed a one-way analysis of variance comparing ONS tissue strain at zero distending pressure following increasing pressures between 5 and 65 mm Hg (in 10-mm Hg steps). The average E at distending pressure of 35 mm Hg was 142±3 mm Hg. Overall, these findings show differences between grouped data (degrees of freedom =6, F=4.19, p=0.001). The pairwise t-test—comparing the strain following nonzero stress level (i.e., 15, 25, 35, 45, 55, and 65 mm Hg) with the strain following the lowest nonzero stress level (5 mm Hg)—shows that zero pressure measurements following deformations of 55 to 65 mm Hg were significantly different from measurements following deformation with 5 mm Hg (p=0.016 and 0.0007, respectively; Fig. 2b, black circles).

When E was recalculated using the value of Ro after a perturbation in distending pressure, pairwise comparison of E for each trial showed a significant difference between the two methods at pressures ≥ 45 mm Hg (Fig. 2b, white versus black circles, asterisks $p < 0.05$).

Discussion

Although a number of clinical studies have attempted to define the optimal ONSD threshold for detecting

elevated ICP, significant heterogeneity in this calculated threshold persists.[1–3] The assumption in such studies is that there is a linear, and therefore elastic, relationship between ICP and ONSD. If heterogeneity exists, from a biomechanical perspective, there are four potential causes: the relationship is in fact not elastic, the elastic properties differ across individuals, plastic deformation affects the measurements, or the model is incomplete and requires the inclusion of other parameters. In this post hoc analysis, we calculated the plastic deformation threshold (one such potential confounder) and characterized the elastic properties of the ONS of previously reported ex vivo and in vivo human data.[7, 8]

The ex vivo results suggest that the E of the ONS is approximately 140 mm Hg. Using results from a clinical study, we have shown that patient-generated ICP and ONS values result in a calculation of E that is approximately the magnitude seen in controlled laboratory conditions. The twofold difference in E between the ex vivo and clinical data sets might have been related to the relatively small changes in distending pressure relative to the ex vivo data, resulting in a greater contribution of measurement error to the calculated E, as well as variation in the optic nerve and trabecular space anatomy between subjects. These results suggest that the Young's modulus is similar to that described for the aorta and saphenous vein.[14, 15]

Evidence of plastic deformation occurs at intraluminal pressures at and above 45 mm Hg. The original

ex vivo study noted that the ONS does not return to the pre-experiment baseline diameter after experiencing pressures ≥45 mm Hg. In this analysis, we support these findings with a more rigorous statistical analysis of the ex vivo data, define biomechanical properties that may account for this observation, and compare the results with a clinical data set. The lack of statistical difference found between the two E calculations at pressures >40 mm Hg for the clinical sample might have been due to the uncontrolled nature of the experiment, including lack of consistent time at the elevated ICP between patients, and the fact that patients did not return to 0 ICP following distension, as in the ex vivo experiment.

Taken together, we believe that these analyses are important for clinical investigators and practitioners. We hypothesize that in patients with raised ICP, unknown exposure to levels above 45 mm Hg will alter the ONSD pressure–volume relationship. Although these ICP values are certainly critical, knowledge of this effect may be helpful when interpreting ONSD for patients who have experienced high ICP before coming to the hospital, such Fig. 2 a Elastic and plastic deformation. The Young's modulus (E) was calculated as the ratio of the change in stress to the change in strain. Plastic deformation caused by high-pressure deformation would result in a subsequent baseline diameter that is larger than the predistension baseline diameter. The slope of the stress–strain curve for the ex vivo data (white circles) is E. The increasing baseline optic nerve sheath diameter in the experiment is a result of plastic deformation (black circles). b Young's modulus (E) and plastic deformation analysis ex vivo. E analyzed from ex vivo data using two calculations of strain: the diameter before distension as the baseline diameter (white circle) and the diameter after distension as the baseline diameter (black circle), with asterisks indicating $p<0.05$ as patients with TBI or an intracranial mass, because their ICP–ONS relationship may not be the same as that in previously healthy patients. Therefore, using ONSD estimations to determine the presence or absence of raised ICP (based on a single threshold value) could be unreliable if former episodes of intracranial hypertension have occurred.

This plastic deformation threshold is supported by electron microscopy findings of ONS tissue injury in swine exposed to ICP of ~40 mm Hg and also explains recent findings in ONSD meta-analyses.[1–3,13] As such, high-pressure exposure to the sheath will show at least some dilation and at the same time may change the elasticity parameters. Tis pathophysiological background should permit screening ONSD in patients experiencing a first episode of elevated ICP.

This study has multiple limitations, however. For example, we were unable to evaluate other potential confounders to the ICP–ONSD relationship, such as the variability in Young's modulus seen across individuals. Given the post hoc nature of our analysis, we were unable to account for other factors that have been shown to affect the ONSD–ICP relationship, such as globe fattening, intraocular pressure, or aspect ratio.[9–11] Further investigation of other elastic properties of the ONSD, such as Poisson's ratio, was not possible in this analysis given the limitation in measurements available, but may be of interest in further studies.

Going forward, there is the practical question of the time course of changes in ONS tissue biomechanical performance: once ONS tissue has been exposed to a high level of ICP, is it no longer useful as a measurement? Our analyses were not able to focus on such time-dependent (time constant) changes in ONS viscoelastic properties because the convenience data sets that we used did not have the appropriate sampling frequency and duration of observations to answer this question.[7,8] Clinical evaluation of all the available examination and imaging data (and not just a single parameter) should remain paramount in the assessment of patients with suspected raised ICP.

Conclusions

In this post hoc analysis, we describe the elastic modulus and threshold for plastic deformation of the ONS. We then validate these calculations with a clinical data set. The ONS has similar elastic characteristics to the aorta and saphenous vein. Furthermore, plastic deformation is likely to occur at ICPs greater than 45 mm Hg on the basis of an ex vivo analysis; however, a clinical analysis failed to demonstrate significance. Future studies should assess the time-dependent viscoelastic properties of the ONS to determine the potential for hysteresis in ONSD measurements.

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Lidocaine also known as lignocaine is a local anesthetic of the amino amide type.

Molar mass:
234.3373 g/mol.

$C_{14}H_{22}N_2O$

Routes of administration:

- Intravenous
- Subcutaneous
- Topical
- Oral

Lidocaïne blocks sodium channels, NMDA receptors, has glycinergic action and reduces the release of substance P

(2,5 mg/ml)

resulting in decreased airway reactivity.* Previous studies have suggested an attenuating effect on the systemic responses to tracheal stimulation when intravenous lidocaine was administered before tracheal stimulation.

CHAPTER 4

Intravenous lidocaine attenuates distention of the optical nerve sheath, a correlate of intracranial pressure, during endotracheal intubation

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Iscander M. Maissan, Rutger V.A. Hollestelle, Koen Rijs, Selma Jaspers, Sanne Hoeks, Iain K. Haitsma, Dennis den Hartog, Robert Jan Stolker

Abstract

Background: By preventing hypoxia and hypercapnia, advanced airway management can save lives among patients with traumatic brain injury. During endotracheal intubation (ETI), tracheal stimulation causes an increase in intracranial pressure (ICP), which may impair brain perfusion. It has been suggested that intravenous lidocaine might attenuate this ICP response. We hypothesized that adding lidocaine to the standard induction medication for general anesthesia might reduce the ICP response to ETI. Here, we measured the optical nerve sheath diameter (ONSD) as a correlate of ICP and evaluated the effect of intravenous lidocaine on ONSD during and after ETI in patients undergoing anesthesia.

Methods: This double-blinded, randomized placebo-controlled trial included 60 patients with American Society of Anesthesiologists I or II physical status that were scheduled for elective surgery under general anesthesia. In addition to the standard anesthesia medication, 30 subjects received 1.5 mg/kg 1% lidocaine (0.15 ml/kg, $ONSD_{lidocaine}$) and 30 received 0.15 ml/kg 0.9% NaCl ($ONSD_{placebo}$). ONSDs were measured with ultrasound on the left eye, before (T_0), during (T_1), and 4 times after ETI ($T_{2\text{-}5}$ at 5-min intervals).

Results: Compared to placebo, lidocaine did not significantly affect the baseline ONSD after anesthesia induction measured at T_0. During ETI, the $ONSD_{lidocaine}$ was significantly smaller (β=−0.24 mm P=0.022) than the $ONSD_{placebo}$. At T_4 and T_5, the $ONSD_{placebo}$ increased steadily, up to 20 min after ETI, but the $ONSD_{lidocaine}$ tended to return to baseline levels.

Conclusion: We found that the ONSD was distended during and after ETI in anesthetized patients, and intravenous lidocaine attenuated this effect.

Introduction:

Traumatic brain injury (TBI) occurs in 50 million people annually worldwide. TBIs have a huge impact on society, due to high medical costs and the loss of productive life years in this relatively young aged, predominantly male patient group. The in-hospital mortality of patients with severe TBI is up to 40%.[1] Of all patients that die of traumas on–scene, 90% have severe TBIs.[2] A primary brain injury that occurs upon mechanical impact can lead to concussion, bleeding, and brain edema, which can result in hypoventilation and hypoperfusion. Then, a so called 'secondary brain injury' occurs, due to cerebral ischemia.[2-4] To prevent secondary brain injuries, specialized on-scene medical treatment is indicated immediately.[3,5]

Treating cerebral hypoxia requires airway management and adequate ventilation to restore arterial oxygen saturation and normal carbon dioxide levels.[2,3] Although endotracheal intubation (ETI) is advocated in patients with trauma that exhibit reduced consciousness (Glasgow Coma Score<9), the ETI outcome of TBIs in prehospital settings depends strongly on the experience and skills of the provider.[3,6] Repetitive manipulation of the trachea during an ETI, even under general anesthesia, may increase intracranial pressure (ICP) and result in a secondary brain injury.[7,8] Consequently, the number of ETI attempts should be minimized.[9]

ICP can be measured by placing an intracranial pressure probe, but this technique is not suitable for prehospital settings. It has been suggested that a sonographic measurement of the optic nerve sheath diameter (ONSD) might provide an accurate, rapid, non-invasive indication of changes in ICP, and thus, the ONSD could be used as a correlate for evaluating the ICP response to ETI.[8,10]

In ear, nose, and throat surgery, intravenous lidocaine is used at the end of the surgical procedure to reduce coughing and gagging in response to the endotracheal tube, as the patient wakes from anesthesia. In the intensive care unit, intravenous lidocaine has been shown to blunt the rise in ICP during laryngeal suction in patients with brain injuries.[11] Therefore, we hypothesized that the ICP response to ETI might be blunted with intravenous lidocaine administered before performing the ETI.

The primary objective of this study was to show that the ONSD, a correlate of ICP, increased during ETI in anesthetized patients. The secondary objective was to evaluate whether intravenous lidocaine attenuated the ONSD response to an ETI.

Methods:

This study was approved by the Medical Ethics Commission of the Erasmus Medical Center in Rotterdam, the Netherlands, and it was conducted according to the declaration of Helsinki (MEC-2017-519).[12]

In this double-blind, randomized, placebo-controlled trial, we included 60 patients over 17 years of age, scheduled for elective surgery under general anesthesia, from July 2019 to November 2020. In accordance with the general requirements for a pilot study, in the absence of sufficient data to conduct a power analysis, we included 30 participants in each treatment group.[13]

Eligible patients had American Society of Anesthesiologists (ASA) I-II physical status, no brain injury, and no self-reported medical history of brain or eye disease. We excluded patients scheduled for head and neck surgery, thoracoscopy, or laparoscopy. We also excluded patients with vasoactive medication or specific contraindications to intravenous lidocaine therapy. We recruited participants one day before an elective surgery. After screening for eligibility, an information form was given to potential participants. Patients were included in the study after providing written informed consent. A computer generated randomization list assigned patients to the lidocaine or placebo group, at a 1:1 ratio.

All patients received standardized general anesthesia induction with 4.0 μg/kg fentanyl, 2.5 mg/kg propofol, and 0.6 mg/kg rocuronium, followed by continuous intravenous anesthesia with 8 mg/kg/h propofol. After the standardized doses of fentanyl, patients in the intervention group received 1.5 mg/kg 1% lidocaine (0.15 ml/kg) intravenous for 3 min prior to ETI. The placebo group received the same amount (0.15 ml/kg) of 0.9% saline, delivered in identical syringes. The study medication was prepared by a nurse that was not further involved in treating the patients and had no access to the operating room. The anesthesia team, the ONSD observer, and the patients were blinded. Study syringes for each patient were labeled with the corresponding randomization number.

After inducing general anesthesia, repeated measurements of the ONSD were performed with sonography through the closed upper eyelid of the left eye. Sonography was performed with an M-Turbo ultrasound device (SonoSite Inc., Bothell, Washington, USA) equipped with a L25× probe, a 13-6 MHz linear array, and an ophthalmic pre-set, with a mechanical index of 0.2. ONSD was measured in the axial plane, at 3 mm behind the retina, as described previously.[8]

The first measurement (T_0) was conducted 3 min after anesthesia was induced and the study medication was administered. The second measurement (T_1) was performed during the ETI, at the exact moment the tube passed the vocal chords. Four subsequent measurements (T_2 to T_5) were performed at 5-min intervals to evaluate “the long-term effect” of the tube between the vocal chords on the ICP.

Statistical analyses

For each group, the means and interquartile ranges of pulse rate, blood pressure (non-invasive), peripheral oxygen saturation, end-tidal CO_2 fraction, and bispectral index values were calculated at each time point (T_0-T_5). A linear mixed model was fitted to the data to estimate the effects of the ETI and lidocaine administration on the ONSD. This analysis method accounted for the dependent nature of repeated measurements in the same participant. Lidocaine administration, time, and the interaction between time and lidocaine (i.e., the effect of lidocaine on ONSD on each point in time), were included as fixed effects. Study participants were included as a random factor. We compared measurements at T_1-T_5 to the baseline ONSD measurement (T_0) and evaluated the effect of lidocaine over time on ONSD. Similar models were fitted to heart rate, mean arterial pressure (MAP), and end-tidal CO_2 to assess whether significant differences existed between the two groups. The assumption of normality was inspected visually with histograms and Q-Q plots. When necessary, data were log-transformed to obtain a better fit with the models. P-values ≤0.05 were considered statistically significant. Statistical analyses were performed with SPSS Statistics (version 26, IBM) and R (version 4.04, the R Foundation).

Results

A total of 90 patients were eligible for participation. Of these, 30 declined (male; 43.3 %, mean age 37.7, range 19-73 years) and 60 were included (male 71.7%, mean age 38.8, range 19-73 years). Vital parameters during the measurements are presented in Table 1.

A total of 360 ONSD measurements were performed. Four measurements were lost, due to technical problems. Therefore, 356 measurements were analyzed. The linear mixed model results (Table 2) showed that lidocaine had no significant effect on the baseline ONSD at T_0 (β=0.04 mm, P=0.803). However, during the ETI (T_1), the ONSD increased significantly (β=0.60 mm, P<0.001). The increase in ONSD at T_1 was significantly smaller in the lidocaine group than that in the placebo group (β=−0.24 mm, P=0.022). ONSD decreased in both groups, after the Macintosh laryngoscope was removed from the larynx and pharynx. At T_2 to T_5, the ONSD remained distended in the placebo group, but it showed a trend towards returning to baseline levels in the lidocaine group. Nevertheless, no significant differences in ONSDs were observed between the placebo and lidocaine groups at T_2 and T_3. At T_4 and T_5, the ONSD was significantly reduced in the lidocaine group (Table 2). Figure 1 shows the effect of ETI on ONSD in both treatment groups over time.

Parameter (IQR)	Group	T_0	T_1	T_2	T_3	T_4	T_5
Heart rate	Lidocaine	70 (64 - 79)	73 (64 - 82)	72 (59 - 80)	70 (60 - 75)	69 (59 - 74)	70 (62 - 80)
Placebo	70 (57 - 87)	72 (61 - 82)	72 (58 - 85)	67 (58 - 75)	67 (55 - 75)	65 (57 - 70)	
MAP (mmHg)	Lidocaine	88 (76 - 100)	79 (63 - 88)	83 (68 - 92)	78 (70 - 87)	78 (69 - 85)	81 (69 - 90)
Placebo	91 (81 - 98)	88 (78 - 99)	88 (76 - 97)	78 (70 - 86)	77 (73- 80)	80 (73 - 90)	
Saturation (%)	Lidocaine	99 (99 - 100)	99 (98 - 100)	99 (98 - 100)	98 (98 -100)	98 (97 - 100)	98 (97 - 99)
Placebo	99 (99 - 100)	99 (99 -100)	99 (99 - 100)	99 (98 -100)	99 (98 - 100)	98 (98 -100)	
End tidal CO_2 (kPA)	Lidocaine	N.a.	N.a.	4.8 (4.7 -5.3)	4.6 (4.3 -4.9)	4.6 (4.2 - 4.8)	4.6 (4.2 - 5.0)
Placebso	N.a.	N.a.	5.0 (4.4 - 5.1)	4.8 (4.5 -5.0)	4.7 (4.3 -5.0)	4.7 (4.4 - 5.1)	
BIS	Lidocaine	34 (26 - 40)	40 (31 - 46)	39 (34 - 42)	36 (29 - 41)	33 (26 - 40)	33 (26 - 37)
Placebo	41 (33 - 47)	38 (27 - 47)	39 (27 - 44)	36 (27 - 47)	24 (26 - 42)	33 (25 - 40)	

Table 1. Vital parameters of the lidocaine and placebo groups at each point in time T_0 = before intubation, but 3 min after anesthesia induction, T_1 = during intubation, T_2 = 5 min after intubation, T_3 = 10 min after intubation, T_4 = 15 min after intubation, T_5 **= 20 min after intubation, bpm = beats per minute, MAP = mean arterial pressure, BIS = bispectral index**

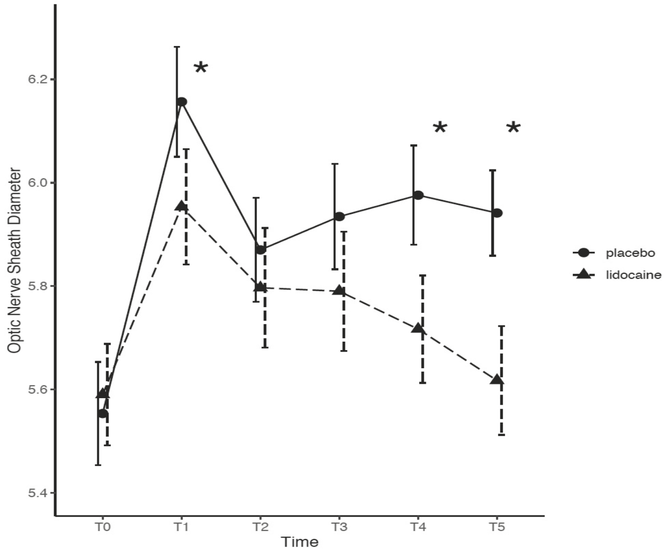

Figure 1. ONSDs measured over time in the lidocaine and placebo groups. Symbols and lines show the means, and error bars indicate interquartile ranges. *P<0.05

Effect	Effect estimate, mm (95% CI)	P value
Placebo T_1	0.60 (0.46 to 0.75)	<0.001*
Placebo T_2	0.32 (0.17 to 0.46)	< 0.001*
Placebo T_3	0.36 (0.22 to 0.51)	< 0.001*
Placebo T_4	0.41 (0.26 to 0.55)	< 0.001*
Placebo T_5	0.37 (0.23 to 0.52)	< 0.001*
Lidocaine T_0	0.04 (- 0.25 to 0.32)	0.80
Lidocaine T_1	-0.24 (-0.44 to -0.04)	0.02*
Lidocaine T_2	-0.11 (-0.31 to 0.09)	0.29
Lidocaine T_3	-0.16 (-0.37 to 0.04)	0.12
Lidocaine T_4	-0.28 (-0.49 to -0.07)	0.008*
Lidocaine T_5	-0.31 (-0.52 to -0.11)	0.003*

Table 2. Linear mixed model results show effect estimates of time and lidocaine on ONSD
Effect estimates of time, lidocaine, and the interaction of lidocaine with time (×) on ONSD were calculated relative to the T_0 of the placebo group (baseline measurement). The T_0 measurement is not displayed, because no effect was expected in the placebo group. *P-values <0.05

Discussion

Our results suggested that intravenous lidocaine subdued the effect of ETI on ONSD (and presumably, ICP) during general anesthesia in patients with ASA I and ASA II status with no cerebral pathology. Changes in ONSD represent changes in ICP, because the optic nerve sheath is anatomically continuous with the dura mater; consequently, cerebrospinal fluid percolates freely in the sheath.[14] As a result, the changes in pressure at the optic nerve are the same as those in the intracranial compartment.[15] The intra-orbital part of the subarachnoid space is most distensible, due to the absence of trabeculae in the sheath.[14] A previous study investigated the reliability of the sonographic ONSD measurement in patients in the ICU, during manipulations of the endotracheal tube; they concluded that the ONSD and ICP were well correlated (R=0.895).[8] A recent systematic review and meta-analysis that focused on this technique showed that the ONSD had high accuracy in diagnosing ICP, with a sensitivity of 90% (CI: 87-92) and a specificity of 88% (CI: 84-91).[16]

We found that the ONSD increased during and after ETI in anesthetized patients without intracranial pathology. After the endotracheal tube was in place, the ONSD decreased, but remained significantly elevated compared to baseline levels. This could be an ongoing response to the ETI, but it was probably due to the continuous stimulation of the trachea and vocal chords by the endotracheal tube in situ.[7] The trachea, carina, larynx, and pharynx are highly innervated by parasympathetic and sympathetic nerves. Airway manipulations result in both defensive reflexes, like coughing and laryngospasms, and systemic responses, like elevated blood pressure and increases in ICP.[17]

Lidocaine blocks sodium channels and NMDA receptors. It is a glycinergic agonist, and it inhibits the release of substance P, which result in reduced airway reactivity.[18] Previous studies have suggested that, when intravenous lidocaine (1.5 mg/kg) was administrated before a procedure, it had an attenuating effect on the systemic responses to tracheal stimulation.[8,19-21] However, a review in 2015 was inconclusive on whether lidocaine could attenuate the ICP response during ETI.[22] Nevertheless, Singh et al. reported that both intravenous dexmedetomidine (0.5 µg/kg) and lidocaine (2 mg/kg) had attenuating effects on the intracranial and systemic hemodynamic responses to tracheal stimulation in patients with severe TBIs. Lidocaine only attenuated the ICP response, but dexmedetomidine also significantly reduced blood pressure and cerebral perfusion pressure (CPP), compared to the values observed at baseline and in the lidocaine group.[11] Previously, lidocaine was also associated with reductions in blood pressure and cerebral blood flow, but at much higher doses (5 mg/kg).[23] In the present study, 1.5 mg/kg lidocaine had no significant effect on hemodynamics, but it did attenuate the ONSD response behind the left eye in patients that underwent ETI. We measured only the ONSD of the left eye, because that transducer position interfered less with the intubation procedure. When we attempted to measure ONSD on the right eye, the transducer blocked the view of the vocal cords.

However, in a previous study, we found that a change in ICP resulted in a simultaneous change in the ONSD behind both eyes.[8] Moreover, Toscano et al. suggested that there was no difference in ONSD distention in the left and right eyes of sedated patients that exhibited increased ICP.[24]

Prehospital intubation (PHI) is advocated for patients with TBIs in several treatment protocols, but it has remained rather controversal.[25,26] Gravesteijn et al. found that ETIs did not significantly benefit a pooled cohort of patients with TBIs in different prehospital systems in Europe.[26] These systems varied, from paramedic-based systems that did not have any medication for performing PHIs, to systems with a physician-based helicopter emergency medical service (HEMS), which in critical cases, assisted a nurse based emergency medical service on-scene with ICP-lowering strategies and medications. In studies by Denninghoff et al. and Bernard et al., drug-assisted PHIs and specialized care during transportation seemed to improve the outcome in patients with severe TBIs, when treated by an anesthesiologist-staffed HEMS.[27,28] Previous studies have suggested that the experience of a caregiver in PHI could significantly influence the mortality of patients with severe TBIs.[6] Indeed, even the smallest improvement in treating severe TBIs that affects the outcome may benefit society, individual patients, and their families.[1] Thus, adding lidocaine to the induction medication for a PHI may benefit patients with severe TBIs.

Study limitations

This study had some limitations. First, our findings on the effects of an ETI on ICP were observed in patients without TBIs; therefore, these findings may not be directly applicable to patients with TBIs, due to altered cerebral autoregulation and increased ICP; however, previous studies have observed attenuating effects of lidocaine during tracheal stimulation in patients with TBIs.[11,17,22] More prospective research is needed on the effects of intravenous lidocaine on ONSD and ICP during ETI in patients with TBIs. Second, intravenous lidocaine seemed to have the potential for reducing ICP, when used as a therapeutic measure, but the exact mechanism remains unclear. Nevertheless, our data showed that hemodynamic values were similar in the lidocaine and placebo groups, which suggested that the effect of 1.5 mg/kg lidocaine was not mediated by the sympathetic system. Third, sonographic ONSD measurements are somewhat limited, partly due to variations among patients in the response to pressure changes, and partly due to intra- and inter-observer variability. Because the composition of connective tissues in the optical nerve sheath varies among patients, the relationship between the ONSD and ICP, although linear, differs between individuals.[15] Therefore, sonographic ONSD measurements should be considered a qualitative, rather than quantitative, tool for evaluating ICP changes.[8] Fourth, we had no reliable means of recording the end-tidal CO_2 in the pre-intubation phase, due to potential air leakage from the mask. Hypo- or hyperventilation, resulting in hypo- or hypercapnia, has been shown to cause deviations in the ONSD.[29] This phenomenon may have influenced the ONSDs measured in the pre-intubation phase, when patients were ventilated manually. Finally, although non-invasive blood pressure measurements were started manually during intubation, the recordings might have missed a spike in blood pressure, due to poor timing.

Conclusion

This study showed that the ONSD, a correlate of ICP, rose during an ETI under general anesthesia in patients without intracranial pathology. Moreover, the persistence of the endotracheal tube between the vocal chords in the trachea resulted in an elevated ONSD for at least 20 min. Intravenous lidocaine attenuated this effect, when performing an ETI under general anesthesia, and during continuous sedation and intubation. More prospective research is needed to confirm our findings on the effect of lidocaine on the ONSD and to determine the ICP response to ETI in patients with TBIs.

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For decades, endotracheal intubation (ETI) has been considered the best way to secure a definitive airway in emergency medicine.

This technique can be lifesaving, but its success depends strongly on the first-pass success rate of the provider.

The aim of the current study is to evaluate the the first-pass endotracheal intubation rate, overall ETI success rate, and accidental unrecognised oesophageal intubation rate for providers with different experience using direct laryngoscopy compared to video laryngoscopy.

CHAPTER 5

The impact of video laryngoscopy on the first-pass success rate of prehospital endotracheal intubation in the Netherlands: a retrospective observational study

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Iscander M. Maissan, Esther van Lieshout, Timo de Jong, Mark van Vledder, Robert Jan Houmes, Dennis den Hartog, Robert Jan Stolker.

Abstract

Purpose: The first-pass success rate for endotracheal intubation (ETI) depends on provider experience and exposure. We hypothesize that video laryngoscopy (VL) improves first pass and overall ETI success rates in low and intermediate experienced airway providers and prevents from unrecognized oesophageal intubations in prehospital settings.

Methods: In this study 3632 patients were included. In all cases, an ambulance nurse, HEMS nurse, or HEMS physician performed prehospital ETI using direct Laryngoscopy (DL) or VL.

Results: First-pass ETI success rates for ambulance nurses with DL were 45.5% (391/859) and with VL 64.8% (125/193). For HEMS nurses first pass success rates were 57.6% (34/59) and 77.2% (125/162) respectively. For HEMS physicians these successes were 85,9% (790/920) and 86,9% (1251/1439). The overall success rate for ambulance nurses with DL was 58.4% (502/859) and 77.2% (149/193) with VL. HEMS nurses successes were 72.9% (43/59) and 87.0% (141/162) respectively. HEMS physician successes were 98,7% (908/920) and 99,0% (1425/1439) respectively. The incidence of unrecognized intubations in the oesophagus before HEMS arrival in traumatic circulatory arrest (TCA) was 30,6% with DL and 37,5% with VL. In medical cardiac arrest cases the incidence was 20% with DL and 0% with VL.

Conclusion: First-pass and overall ETI success rates for ambulance and HEMS nurses are better with VL. The used device does not affect success rates of HEMS physicians. VL resulted in less unrecognized oesophageal intubations in medical cardiac arrests. In TCA cases VL resulted in more oesophageal intubations when performed by ambulance nurses before HEMS arrival.

Introduction

For decades, endotracheal intubation (ETI) has been considered the best way to secure a definitive airway in emergency medicine. This technique can be lifesaving, but its success depends strongly on the first-pass success rate of the provider.[1] This rate in turn depends on provider experience and exposure,[1-3] with limited experience associated with a two-fold increase in mortality among patients with traumatic brain injury.[4] A UK study identified an overall ETI success rate of 64% among paramedics, with an unrecognised oesophageal intubation rate of 11%.[5]

These and other findings have led to the introduction of alternative airway techniques such as supraglottic airway devices in Scandinavian and British paramedic based emergency medical service (EMS) systems.[6,7] The new European Resuscitation Council (ERC) guidelines state that only experienced providers should perform advanced airway management during cardiopulmonary resuscitation (CPR).[8] Less experienced providers should use a supraglottic airway device or perform mask bag ventilation during CPR. In the Netherlands, in contrast to paramedic-based EMS systems in other western countries, specialised nurses staff the ambulances. Data are limited on prehospital intubation success rates in the Netherlands, including comparisons among ambulance nurses, helicopter EMS (HEMS) nurses and HEMS physicians and by direct versus video laryngoscopy.[9,10]

The aim of the current study is to evaluate the first-pass endotracheal intubation rate, overall ETI success rate, and accidental unrecognised oesophageal intubation rate for providers with different experience using direct laryngoscopy compared to video laryngoscopy.

Methods

This retrospective observational cohort study covers a 6-year period (1 January 2014 to 31 December 2020) using data from the Rotterdam physician-staffed HEMS (P-HEMS) database. The medical ethical commission of the Erasmus Medical Center Rotterdam approved a waiver for this study (MEC-2021-0243).

All consecutive patients were included, and all underwent ETI by direct or video laryngoscopy in the prehospital setting, performed by an ambulance nurse, HEMS nurse, or HEMS physician. Ambulance nurses used the direct or video laryngoscope provided by their ambulance service. HEMS nurses and physicians could choose either at their discretion. Patients with missing data on the number of intubation attempts or tube position were excluded.

The primary outcome measure was the first-pass ETI success rate for each of the three provider groups using direct or video laryngoscopy. Secondary outcome measures were the overall ETI success rates and the rate of unrecognised oesophageal intubation in the three groups using direct or video laryngoscopy. First-pass ETI was defined as a successful placement of a tube in the trachea at the first attempt. An ETI attempt was defined as any attempt in which the laryngoscope blade was passed beyond the lips of the patient. Overall ETI success rate was defined as an effective endotracheal intubation by one provider after one or more attempts. Unrecognised oesophageal intubation was defined as a tube located in the oesophagus by the next airway provider (re)assessing the airway.

Experience with ETI differs among individual Dutch ambulance nurses because of variability in training and prior experience in intensive care, emergency care, or anaesthesia nursing. Before joining an EMS, all nurses undergo an initial 8 month prehospital emergency care training program. If the candidate has no previous airway training or experience, they will be signed up for an ETI training in the operating theatre in an affiliated hospital. These trainings vary from 3 to 8 days depending on logistics and the schedules of the EMS and the hospital. Average prehospital exposure is 3–6 ETI's per ambulance nurse per year.[9] The availability of refresher courses or extra training in airway management is a matter of individual or local priority. Some services invite HEMS physicians or anaesthesiologists to provide additional teaching, training, and tips and tricks, but these additions are not standardised. Dutch EMS vehicles are equipped with a bag-mask-valve, laryngeal masks, Macintosh or video laryngoscope, and tubes for non–drug-assisted ETI.

HEMS nurses have previous ETI experience in their role as an ambulance nurse and perform all their HEMS intubations under supervision of a HEMS physician. Their yearly ETI exposure is around 10–15 cases.

The Rotterdam HEMS crew includes anaesthesiologists (n=10) with considerable experience in airway management (>3000 ETIs) or trauma surgeons (n=2) with extensive initial HEMS training (>300 ETIs) in airway management. Yearly exposure to ETI in prehospital settings exceeds 50 per physician. In addition to the standard ambulance equipment, HEMS physicians can administer all advanced airway interventions including prehospital induction of anaesthesia and surgical airway placement. All intubations by ambulance nurses or HEMS nurses in this study that were supervised by a HEMS physician patients received proper medication if indicated. To evaluate the position of the tube, HEMS and ground EMS use end-tidal CO_2 monitoring and clinical evaluation to confirm tracheal placement after ETI. Most intubations in this study by ambulance nurses and HEMS nurses under supervision of a HEMS physician were drug assisted. Only some medical cardiac arrest patients were intubated without medication. All ETI attempts by ambulance nurses before HEMS arrival were non-drug assisted intubations.

The Rotterdam HEMS is dispatched via the ambulance dispatch centre of Rotterdam. Dispatch can be primary, based on caller information about the mechanism of injury or the patient's clinical condition, or secondary if the ambulance crew requests extra medical support on-scene by a HEMS nurse and physician.

The Netherlands is a densely populated small, well developed country with a high density of hospitals. The mean distances to a level 1 trauma center is about 30 km by road. The Rotterdam HEMS annually transports about 3% of their prehospital patients by helicopter. The other patients are transported by road ambulances. If necessary the HEMS physician will escort the patient after stabilization on scene during the ambulance transportation together with the ambulance nurse.

Statistical analysis

Statistical analysis was performed using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Normality of continuous data was tested with the Shapiro–Wilk test, and homogeneity of variances was tested using the Levene's test. Data are reported per group (i.e., intubation by ambulance nurse, HEMS nurse, or HEMS physician). Because all continuous data deviated from normal distribution, we have used the Mann–Whitney U-test for differences among groups and reported the results as medians with quartiles (Qs). Categorical data are reported as numbers with percentages, and differences across groups were tested using the Chi-squared test.

Results

A total of 3821 patients underwent one or more ETI attempts in the prehospital setting during the study period. Of those, 189 (4.9%) had missing data for first-pass success, identification of the provider performing the intubation, or number of intubation attempts and were therefore excluded from analysis for first-pass success (Figure 1). Demographic data for the remaining 3632 patients are shown in Table 1.

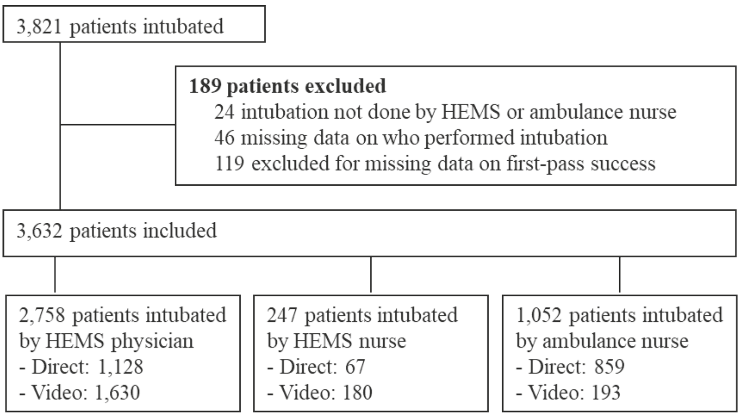

Figure 1. Study flowchart

	All intubations (n=3632)		HEMS physician (n=2758)		HEMS nurse (n=247)		Ambulance nurse (n=1052)	
	n		n		n		n	
Male	3632	2414 (66.5)	2758	1853 (67.2)	247	162 (65.6)	1052	694 (66.0)
Median age (years)	3632	51 (30–67)	2758	50 (29–66)	247	53 (33–69)	1052	53 (35–68)
Trauma	3632	1848 (50.9)	2758	1467 (53.2)	247	120 (48.6)	1052	449 (42.7)
Primary dispatch	3591	2597 (72.3)	2726	2002 (73.4)	246	174 (70.7)	1040	712 (68.5)
Cardiopulmonary resuscitation	3632	1345 (37.0)	2758	989 (35.9)	247	75 (30.4)	1052	535 (50.9)
Traumatic cardiac arrest	3632	367 (10.1)	2758	271 (9.8)	247	19 (7.7)	1052	157 (14.9)
Medical cardiac arrest	3632	978 (26.9)	2758	718 (26.0)	247	56 (22.7)	1052	378 (35.9)

Table 1. Demographics of the study population, grouped by type of provider performing the endotracheal intubation
Data are shown as n (%) or as median (P_{25}-P_{75}). HEMS, Helicopter Emergency Medical Services.

	All intubations (n = 3632)		HEMS physician (n=2758)		HEMS nurse (n=247)		Ambulance nurse (n=1052)	
	n		n		n		n	
ETI indication								
Glasgow Coma Scale < 8	3214	1576 (49.0)	2459	1223 (49.8)	224	120 (53.6)	923	351 (38.0)
Cardiopulmonary resuscitation		1345 (41.8)		989 (40.2)		75 (33.5)		535 (58.0)
(Partial) airway obstruction		189 (5.9)		164 (6.7)		20 (8.9)		16 (1.7)
Severe agitation		51 (1.6)		42 (1.7)		6 (2.7)		6 (0.7)
Airway oedema		40 (1.2)		32 (1.3)		2 (0.9)		10 (1.1)
Foreign body		13 (0.4)		9 (0.4)		1 (0.4)		5 (0.5)
Intubation prior to HEMS arrival	1270	246 (19.4)	N.A.	N.A.	N.A.	N.A.	1052	246 (23.4)

Table 2. Indications for endotracheal intubation, grouped by type of provider performing the procedure
Data are shown as n (%). ETI, endotracheal intubation; HEMS, Helicopter Emergency Medical Services; N.A., not applicable.

The median age was 51 (Q1–Q3, 30–67) years, with a wide range of 0 to 100 years. The indication for most intubations was a Glasgow Coma Scale < 8 (n=1576; 49.0%) and CPR (n=1345; 41.8%; Table 2). Patient characteristics and indication for ETI were similar between the direct and video laryngoscopy groups.

First-pass ETI success rate

First-pass ETI success rates in the entire group were 49.0% (516/1052) for ambulance nurses 71.9% (159/221) for HEMS nurses and 86.5% (2041/2359) for HEMS physicians.

First-pass ETI success rates with direct laryngoscopy were 45.5% (391/859) and with video laryngoscopy 64.8% (125/193); p<0.0001) for ambulance nurses.

First-pass ETI success rates with direct laryngoscopy were 57.6% (34/59) and with video laryngoscopy 77.2% (125/162); p = 0.0042) for HEMS nurses.

First-pass ETI success rates with direct laryngoscopy were 85.9% (790/920) and with video laryngoscopy 86.9% (1251/1439); p = 0.488) for HEMS physicians. (Table 3).

Overall ETI success rates

Overall ETI success rates in the entire group were 61.9% (651/1052) for ambulance nurses 83.3% (184/221) for HEMS nurses and 98.9% (2333/2359) for HEMS physicians.

With direct laryngoscopy overall intubation success rates were 58.4% (502/859) and with video laryngoscopy 77.2% (149/193); p<0.0001) for ambulance nurses.

Overall intubation success rates with direct laryngoscopy were 72.9% (43/59) and 87,0%(141/162); p = 0.0133) with video laryngoscopy for HEMS nurses. (Table 3)

Overall intubation success rates with direct laryngoscopy were 98.7% (908/920) for HEMS physicians. With video laryngoscopy the overall success rates for HEMS physicians was 99.0% (1425/1439); p = 0.499). (table 3).

In table 4 we describe the first pass and overall success rate per provider and per device used for ETI after prior attempts by another airway provider. After previous attempts of the ambulance nurses the first pass success of the HEMS nurses and HEMS physicians are lower. The overall success of HEMS nurses in this group is lower as well but the overall success for HEMS physicians was more or less the same as in table 3. (p = 0.19)

When HEMS nurses failed to intubate, the first pass success of HEMS physicians was significantly (p<0.0001) lower but the overall success was only slightly (p=0.045) lower than in table 3. HEMS physicians had lower overall success rates with video laryngoscopy 92.9% (26/28) in patients with prior attempts by other airway providers compared with making their own first attempt 99.0% (1425/1439); p=0.0024; Table 4)

	HEMS physician		HEMS nurse		Ambulance nurse	
	n		n		n	
All intubations, n (%)						
First-pass success	**2359**	**2041 (86.5)**	**221**	**159 (71.9)**	**1052**	**516 (49.0)**
Direct laryngoscopy	920	790 (85.9)	59	34 (57.6)	859	391 (45.5)
Video laryngoscopy	1439	1251 (86.9)	162	125 (77.2)	193	125 (64.8)
Overall success	**2359**	**2333 (98.9)**	**221**	**184 (83.3)**	**1052**	**651 (61.9)**
Direct laryngoscopy	920	908 (98.7)	59	43 (72.9)	859	502 (58 4)
Video laryngoscopy	1439	1425 (99.0)	162	141 (87.0)	193	149 (77.2)

Table 3. First-pass and overall success of ETI in prehospital setting in the Netherlands in patients in whom no previous attempt was made, grouped by type of provider performing the ETI and by device Data are shown as n (%). ETI, endotracheal intubation; HEMS, Helicopter Emergency

	HEMS physician		HEMS nurse		Ambulance nurse	
	n		n		n	
All intubations, n (%)						
First-pass success	**362**	**288 (79.6)**	**26**	**12 (46.2)**	N.A.	N.A.
Direct laryngoscopy	192	161 (83.9)	8	5 (62.5)	N.A.	N.A.
Video laryngoscopy	170	127 (74.7)	18	7 (38.9)	N.A.	N.A.
Overall success	**362**	**355 (98.1)**	**26**	**14 (53.8)**	N.A.	N.A.
Direct laryngoscopy	192	190 (99.0)	8	5 (62.5)	N.A.	N.A.
Video laryngoscopy	170	165 (97.1)	18	9 (50.0)	N.A.	N.A.

Intubations by HEMS physician after failed ETI by HEMS nurse

	HEMS physician		HEMS nurse		Ambulance nurse	
	n		n		n	
All intubations, n (%)						
First-pass success	**46**	**30 (65.2)**	N.A.	N.A.	N.A.	N.A.
Direct laryngoscopy	18	14 (77.8)	N.A.	N.A.	N.A.	N.A.
Video laryngoscopy	28	16 (57.1)	N.A.	N.A.	N.A.	N.A.
Overall success, all intubations	**46**	**44 (95.7)**	N.A.	N.A.	N.A.	N.A.
Direct laryngoscopy	18	18 (100.0)	N.A.	N.A.	N.A.	N.A.
Video laryngoscopy	28	26 (92.9)	N.A.	N.A.	N.A.	N.A.

Table 4. Intubations after previously failed ETI. Intubations by HEMS physician or HEMS nurse after failed ETI by ambulance nurse.
ETI, endotracheal intubation; HEMS, Helicopter Emergency Medical Services; N.A., not applicable Medical Services.

Unrecognised oesophageal intubation

The database also contained information on oesophageal intubation in patients already intubated before HEMS arrival. Ambulance nurses intubated 246 patients before HEMS arrived on scene. In this subgroup of 246 patients, 17.1% (42/246) had an unrecognised oesophageal intubation, requiring intervention by a HEMS physician. In traumatic circulatory arrest cases a substantial number of patients was intubated in the oesophagus with both direct (37.5%) and video (30.6%) laryngoscopy. If direct laryngoscopy was used for intubating patients in medical cardiac arrest, 20% of attempts resulted in unrecognised oesophageal intubations. If video laryngoscopy was used in medical cardiac arrest cases, no unrecognised oesophageal intubations were reported (Table 5).

	n	malposition
All intubations (all indications)	**246**	**42 (17.1%)**
Traumatic circulatory arrest	65 (26.4%)	21 (32.3%)
Medical CPR	115 (46.7%)	18 (15.7%)
Other	66 (26.8%)	3 (4.5%)
All intubations for traumatic circulatory arrest	**65**	**21 (32.3%)**
Direct laryngoscopy	49	15 (30.6%)
Video laryngoscopy	16	6 (37.5%)
All intubations for medical CPR	**115**	**18 (15.7%)**
Direct laryngoscopy	90	18 (20.0%)
Video laryngoscopy	25	0 (0.0%)

Table 5. Prehospital intubations by ambulance nurse prior to HEMS arrival and percentage of unrecognized esophageal intubations (malposition)

All intubations by HEMS nurses reported in this study were performed under direct supervision of the HEMS physician, and no oesophageal intubations occurred in this group. One patient was intubated in the oesophagus by a HEMS physician (1/2459; 0.0004%) which was recognized by the anaesthesiologist of the trauma team in the receiving hospital.

Discussion

The results of this study show a higher first pass and overall success rate for ETI by HEMS physicians than HEMS nurses and ambulance nurses. HEMS nurses performed better than ambulance nurses in both first pass and overall success rate. This indicates a beneficial effect of provider experience and exposure in first pass and overall success rates of ETI in prehospital setting.

Both HEMS nurses and ambulance nurses had a higher first pass and overall success rate with videolaryngoscopy compared to direct laryngoscopy. For HEMS physicians the type of device used for ETI did not affect their first pass or overall intubation success rate.

In contrast, with our results, Breeman et al. reported that the use of video laryngoscopy did not improve first-pass success rates and only slightly increased the overall success rate during CPR for medical cardiac arrests in their cohort of Dutch ambulance nurses intubating without supervision of a HEMS physician.[10]

Of all 1052 intubations performed by ambulance nurses 246 patients (23,3%) were intubated before HEMS arrival. Despite the use of end tidal CO_2 measurement 17.5% (43/246) of patients were intubated and ventilated in the oesophagus. (Table 5) Of these cases 73,1% (180/246) were in a circulatory arrest (Traumatic circulatory arrests or medical cardiac arrests) in which $ETCO_2$ levels are lower and probably less predictive for correct tube position. In cases of traumatic arrests the video laryngoscope resulted in more unrecognized oesophageal intubations than direct laryngoscopy. Blood and other secretions may have covered the lens making the Mc Graft laryngoscope just an ordinary direct Macintosh laryngoscope. The incidence of oesophageal tubes in traumatic circulatory arrests was 30.6% (15/49) when a direct laryngoscope was used and 37.5% (6/16) after video laryngoscopy. Intubation with a direct laryngoscope in cases of medical cardiac arrest resulted in 20% unrecognized oesophageal intubations. All malpositioned tubes were repositioned after HEMS arrival. One should be cautious in drawing conclusions because the numbers are low in this subgroup but video laryngoscopy seems to lower the frequency of unrecognised oesophageal intubations during CPR for 25 registered cases in medical cardiac arrest.

In Dutch prehospital care, two ambulances are dispatched for medical cardiac arrest, without the primary assistance of HEMS. The Difficult Airway Society and the recently published ERC guidelines advise airway management with supraglottic devices or bag-valve-mask ventilation during CPR by pre hospital personal based on the results of the AIRWAYS-2 trail.[8,11,12] This study was performed in the United Kingdom (UK) including nearly 9300 adults in medical cardiac arrest in need of airway management during CPR. No significant difference on patient outcome was found between supraglottic airway devices and endotracheal tubes.[11]

These paramedics in the UK, with no prior medical education, have a 30-month initial training programme with a 2 week hospital placement in which they have to perform 20-25 ETI's under direct supervision. In contrast Dutch ambulance nurses may have more experience in airway management if they have had prior exposure as an anaesthesia nurse. However the colleague's with prior experience at an intensive care unit or emergency department have less previous experience in advanced airway management and are less skilled than their colleagues from the UK in ETI. From that perspective the

Dutch protocols should be adjusted to the new ERC guidelines as well when it comes to airway management by these lower skilled colleagues.

If the Dutch EMS decides for some reason to stick to the current approach; ETI as their first choice during CPR, the training of the providers should be greatly expanded to increase the first pass and overall success rates. Reduced physiological reserves in critically ill patients contributes dramatically to added risks in non-elective settings, causing profound peri-intubation hypoxia, arrhythmia, cardiac arrest, and death.[13] Repetitive ETI attempts during CPR may take away effort and attention from uninterrupted thoracic compressions and electrical defibrillation.[8]

Buis et al. found that a threshold of 50 ETIs with direct laryngoscopy in elective circumstances is needed to reach a success rate of 90% in one or two attempts.[14] Prior exposure of at least 240 intubations with direct laryngoscopy is required to achieve a 90% success rate during CPR.[15] As to the results of our study, using video laryngoscopy instead of direct laryngoscopy may improve the first pass and overall success rates with limited prior exposure. One can argue if the current exposure of 3-6 intubations a year for ambulance nurses in the Netherlands is enough to prevent from so called skill atrophy. Prehospital use of laryngeal masks during CPR has been studied in the Dutch EMS before and seems viable.[6,7,11,16] The first attempt success of insertion of a laryngeal mask by Dutch ambulance nurses is up to 98% and the incidence of regurgitation and aspiration in the ETI and the LMA group were not significantly different in the AIRWAY-2 trial.[7,11,16]

Although most airways can be managed with supra glottis airway devices, some need urgent intubation when the LMA doesn't fit good enough and bag-mask-valve ventilation is ineffective. Concentration of advanced airway management skills in a selected group of prehospital care workers like physician-staffed-HEMS or within the EMS like solo rapid responders or physician assistants with previous experience in anesthesia or excessive training may increase annual ETI provider exposure and may increase ETI success rates in cases a LMA is not suitable. This would match the system on the emergency departments in the Netherlands. The Dutch commission for healthcare audit and inspection stated that an advanced airway provider in the emergency department should be on scene in 15 minutes and should have previous experience and an exposure of at least 50 (non)elective ETI's a year to be considered current in airway management in non-elective emergency settings.[17] Providers without such exposure should focus on bag-mask-valve ventilation. If this technique fails a LMA can be inserted to optimize ventilation conditions until an airway expert arrives and can intubate the patient.

Capnography is the gold standard for confirming endotracheal tube position, even in a CPR scenario. After its introduction in anaesthesia the number of unrecognized oesophageal intubations decreased dramatically even in cases where bilateral breath sounds were heard, no borborygmus was heard, fogging of the tube and symmetric thoracic movements were observed.[18,19]

Although capnography was used in all medical CPR cases in this study, 20% of patients that were intubated under direct laryngoscopy prior to HEMS arrival had an unrecognised oesophageal tube position. The HEMS database does not contain information to explain why these tube malposition's went unrecognised despite the use of capnography. From case debriefings, HEMS nurses and physicians recall that the medical condition of the patient or equipment failure was mentioned as the cause of the absence of end-tidal CO_2. Because the tube position, was never doubted more training for ambulance nurses is needed in interpreting $ETCO_2$ waveforms as well.[17] In all patients intubated by or under supervision of a HEMS physician $ETCO_2$ curves were evaluated in the field and reported in the database to prove the correct tube position. If tube position was doubted tubes were taken out and bag-mask-valve ventilation was continued until another intubation attempt resulted in a tracheal tube position confirmed with $ETCO_2$ waveforms. In the case of unrecognized oesophageal intubation by a HEMS physician the position was evaluated by auscultation and capnography. Bilateral breath sounds were heard after intubation but were in fact referred sounds from air moving up and down the oesophagus.[20] The first capnography waveforms registered directly after intubation probably were attributable to gastric carbon dioxide. After quick evacuation from the hazardous situation in which the trauma patient and the (H)EMS crew were at the time of intubation, a reassessment showed no capnographic waveform anymore. Tube position was not doubted and alternative causes for the absence were treated (e.g., tension pneumothorax and hypovolaemia).

Some Dutch ambulance nurses with limited experience currently use laryngeal masks the provided device. Ambulance nurses with prior training in anaesthesia are more experienced in ETI and one can assume they may provide better care by handling a laryngoscope.[14] One region in the Netherlands has changed the protocol and made laryngeal masks the only option for airway management because of low ETI success rates with direct laryngoscopy. In addition, because video laryngoscopy is often thought to improve intubation success rates among low- and intermediate-skilled airway providers, some services have equipped their ambulances with video laryngoscopes.[21] According to our results, equipping all Dutch ambulances with video laryngoscopes could reduce unrecognised oesophageal tube placements by ambulance nurses during medical CPR. Based on the other results in this study the success rates with both direct and video laryngoscopy by ambulance nurses with the current training programme are too low to continue the practise of ETI in CPR cases by ambulance nurses.

Limitations

This is a retrospective database study caring the risk of several biases and confounders. Furthermore the population in this study does not represent the entirety of patients intubated in the prehospital setting because HEMS is not dispatched for all CPR scenarios in adult patients. Relevant issues on anatomy (small mouth opening, small mandibles, small thyromental distance) or injury related challenges (fractures of the jaw teeth or CWK) aren't registered in the database. This may introduce a bias of more complex cases in the HEMS database. Nevertheless the reported first-pass success rates with direct laryngoscopy by Breeman et al. in medical CPR cases without a HEMS crew on scene shows more or less the same first-pass successes rates as in this study. The first-pass successes rates especially in patients primarily intubated by HEMS nurses or HEMS physicians may be lower due to selection bias of more complex cases in which EMS asked for P-HEMS assistance.

Moreover, we had no information on the previous experience of the individual ambulance nurse, HEMS nurse and HEMS physician and included them as groups although their experience and exposure may vary. In the group of HEMS physicians there were no differences in first-pass and overall success rates, but in previous literature on our team, trauma surgeons tended to be more reluctant to perform ETI than anaesthesiologists in similar cases.[22] Furthermore, if intubation is indicated, trauma surgeons tend to perform the ETI themselves instead of supervising an ambulance nurse or HEMS nurse in the procedure. This may lead to a different patient selection.

Missing data in the database also confer a risk of bias although the excluded cases did not differ from the included cases in patient characteristics. In addition, these findings are consistent with a previous retrospective report by Peters et al., concerning first-pass success in Dutch prehospital care and with international results on unrecognised oesophageal intubations.[5,9]

In our HEMS operation, the choice for direct or video laryngoscopy was at the discretion of the provider, which could be a source of bias as well. Even more because we had no data on whether video laryngoscopy was used as a rescue strategy when direct laryngoscopy failed or vice versa. Ambulance nurses didn't have a choice between these devices and had to work with the equipment supplied by their company if HEMS was not at the scene. However, for all providers, the first-pass success rates in the video laryngoscopy group were better than in the direct laryngoscopy group under supervision of a HEMS physician. Most patients were intubated on scene in the position in which they were found with limited adjustments in positioning if no cervical spine fractures were suspected. The standardised positioning on a trolley and protocolized intubation procedures as used in the UK is not a standard operating procedure in the Netherlands.

Conclusion

First-pass and overall success rates for ETI by ambulance nurses and HEMS nurses are higher with video laryngoscopy than direct laryngoscopy. The incidence of unrecognised oesophageal intubation in cases intubated before HEMS arrived was 17,5%. The incidence in cases of circulatory arrest was higher than in circulating patients. The incidence in cases of medical cardiac arrest intubated with direct laryngoscopy was 20%. None were reported in EMS regions using video laryngoscopy for ETI during medical cardiac arrests. In traumatic circulatory arrest the incidence was higher with video laryngosopy than with direct laryngoscopy. Despite the higher first pass and overall success rates with videolaryngoscopy, the success rates are too low to justify the current approach of airway management with ETI by ambulance nurses in the Netherlands. If training cannot be increased to improve success rates with direct or video laryngoscopy, LMA's should be preferred by Dutch ambulance nurses as the first choice in prehospital airway management.

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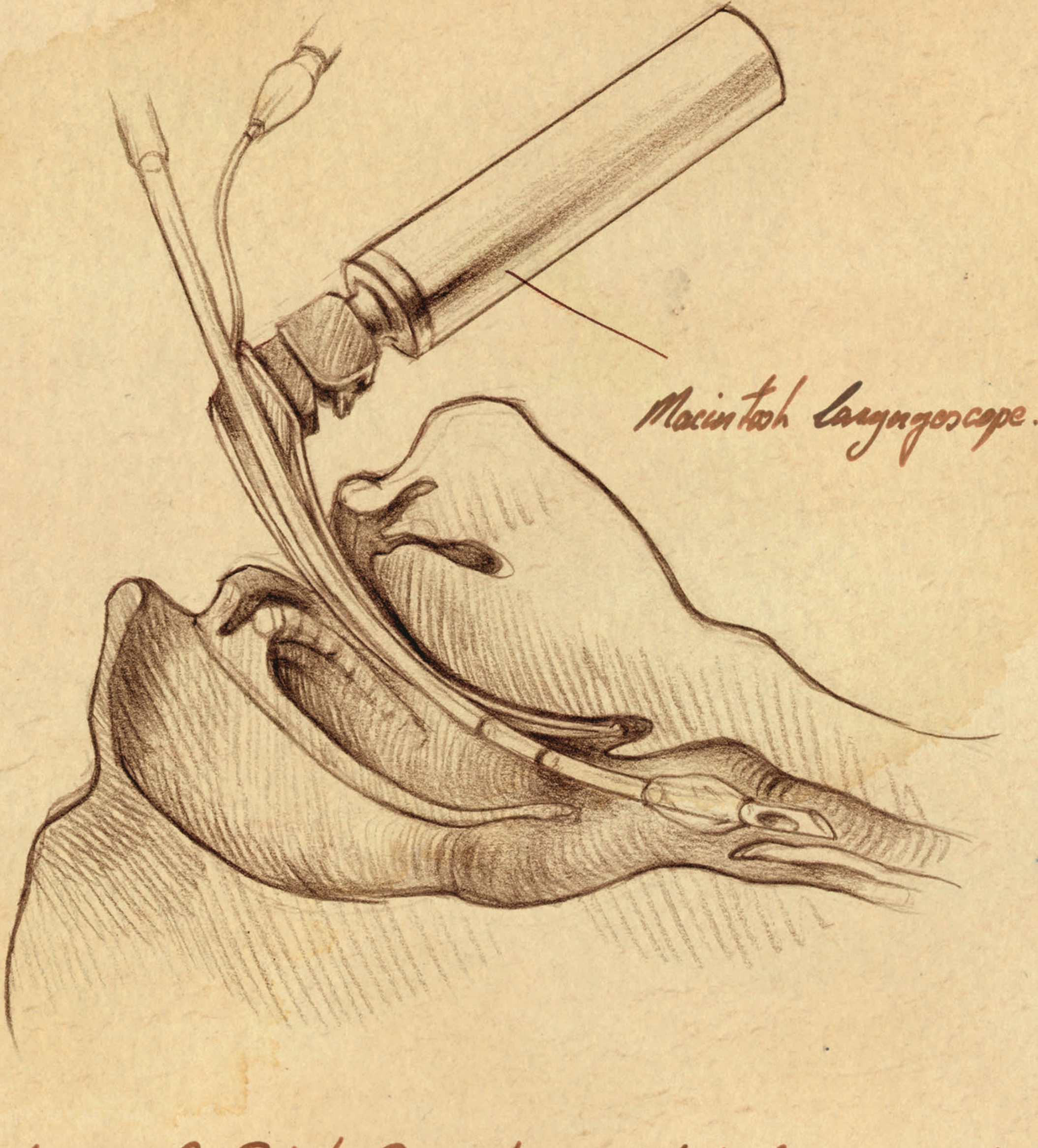

In 1943 Sir Robert Reynolds Macintosh (1897 - 1989) discovered the principle of direct elevation of the epiglottis and developed the laryngoscope which bears his name.

CHAPTER 6

Defining the learning curve for endotracheal intubation using direct laryngoscopy: a systematic review

Resuscitation 2016;99:63-71.

Maria L Buis, Iscander M Maissan, Sanne E Hoeks, Markus Klimek, Robert Jan Stolker

Abstract

More than two failed intubation attempts and failed endotracheal intubations (ETIs) are associated with severe complications and death. The aim of this review was to determine the number of ETIs a health care provider in training needs to perform to achieve proficiency within two attempts. A systematic search of the literature was conducted covering the time frame of January 1990 through July 2014. We identified 13 studies with a total of 1,462 students who had attempted to intubate 19,108 patients. This review shows that in mostly elective circumstances, at least 50 ETIs with no more than two intubation attempts need to be performed to reach a success rate of at least 90%. However, the evidence is heterogeneous, and the incidence of difficult airways in non-elective settings is up to 20 times higher compared to elective settings. Taking this factor into account, training should include a variety of exposures and should probably exceed 50 ETIs to successfully serve the most vulnerable patients.

Introduction

Failed intubation is the most frequently reported complication in airway management according to a recent British survey.[1, 2] Numerous (>2) attempts and failed endotracheal intubations (ETIs) are associated with oxygen desaturation, arrhythmias, cardiac arrest, brain damage, and mortality.[3-6] The most critical patients deserve the best-skilled health care providers, and the more experienced the physician, the higher the chance of a successful intubation.[7] As for all manual skills, ETI is subject to a learning curve.[8]

ETI skills should be developed in a structured training program, which is especially relevant for those who intubate in non-elective or emergency settings where the incidence of a difficult or failed intubation is up to 20 times higher than in the elective setting.[3] In the Netherlands, training programs for non-anaesthesiologists who perform ETIs currently do not require a minimum number of completed ETIs.[9]

The aim of the present study was to provide a systematic review of the literature on the learning curve for ETIs. Because direct laryngoscopy (DL) is the most widely used technique pre-hospital and in-hospital, we reviewed the learning curves for this procedure. We specifically aimed to identify the number of ETIs a novice intubator must perform to achieve proficiency with this procedure, defined as successfully intubating within two attempts.

Methods

Study selection

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A search of the literature (January 1990–July 2014) was performed using EMBASE, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed. The following keywords were used for the search: 'intubation', 'learning curve', and 'laryngoscopy'. The search was limited by excluding the keywords 'videolaryngoscopy' and 'paediatrics'. The full electronic searches can be found in the appendix. In addition, we hand searched the reference sections of all articles that were selected for review.

Inclusion criteria were English-language only, human studies only, DL as the sole procedure, novice participants or number of previously performed intubations clearly identifiable, and specified quantification of the success rate learning curve for ETI. Studies were excluded if they had been conducted in a simulation laboratory, were limited to paediatric patients only, involved ETI using a technique other than DL (e.g., videolaryngoscopy, fiber optic intubation), did not include all ETIs in the success rate learning curve, were review articles, technique papers letters, case reports, comments, or editorials, or if full text was not available.

Data collection and analysis

An electronic data collection form (Microsoft Excel 2011) was used to extract data including number of intubations and students per study, stop criteria for the intubation attempts per patient (predefined number of attempts, time limit or potentially harmful situation at which point the supervisor took over the procedure), statistical analysis of the learning curve, overall success rate, and complications. Two reviewers (M.B. and I.M.) independently identified potentially relevant articles, first by title and abstract and afterwards by full text. Any disagreements were discussed and resolved by consensus. Because of differing outcome measures reported by the included studies, meta-analysis of data was not considered appropriate.

Data definitions

The definition of an ETI is the insertion of the laryngoscope blade and/or endotracheal tube in the oropharynx. The term 'per patient attempt' implies each attempt at ETI in a single patient. 'Per student attempt' refers to the total amount of successful or non-successful intubations performed per student.

Cumulative success rates of 80% and 90% were extracted, if possible, from the included studies. These cumulative success rates indicate the percentage of successful intubations including previous intubation attempts per student. The cut-off points of 80% and 90% were chosen given their frequent use in the literature.[8, 10-14]

Possible biases

Since there is a lack of validated quality assessments of learning curve studies or reviews, we broadened our search. We studied the prevalence of the success rates of students and applied a validated quality assessment.[15] The explanation per question is listed below the quality assessment. For each publication, each item was rated as **Yes** for low risk of bias and **No** for high risk of bias.

Results

Study selection

A total of 1,689 articles were identified by the search after removal of duplicates. Finally, a total of 13 studies were included in this systematic review. See Figure 1 for the PRISMA flowchart.

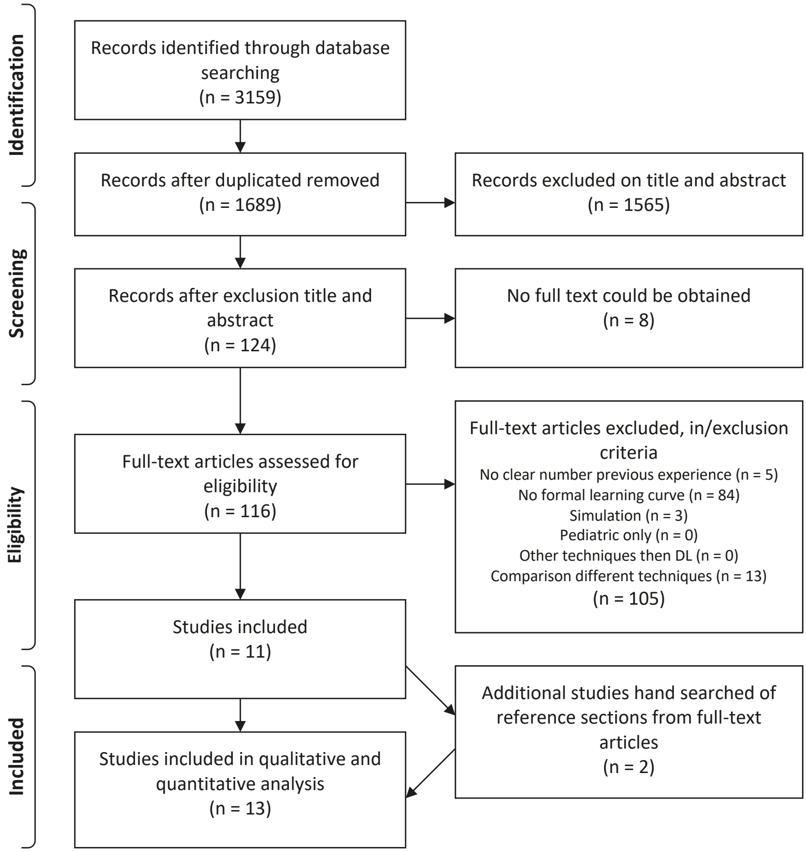

Figure 1: Flow chart selection studies

Study characteristics

Table 1 lists the descriptive characteristics of the included studies. The data of Levitan et al. were split into two separate groups because they had two groups of students with different interventions, as we highlight later.[16] The 13 studies had a total of 1,462 students, varying from 7 to 891 students per study. Combined, these articles included 19,108 patients.

The students were first-year residents, medical students or paramedic students without previous experience. In three studies, some students had limited experience with performing ETIs on patients. These intubation attempts were included within the learning curves of these studies.[11, 17, 18]

Study	Date	Design	Background students	No. Participants	No. Patients	Stop criteria
Bernhard et al. [17]	2012	Prospective	Anaesthesiology residents	21	3404	Unknown
Chao et al.[22]	2013	Retrospective	Medical students	94	927	3 attempts or any harmful situation
Komatsu et al.[14]	2010	Prospective	Medical interns	15	679	2 attempts
Konrad et al.[8]	1998	Prospective	Anaesthesiology residents	11	990	2 attempts
Kopacz et al.[12]	1996	Prospective	Anaesthesiology residents	7	86	Unknown
Levitan et al.[16]	2001	Retrospective	Paramedic students	113	783	Unknown
Levitan et al.[16]	2001	Prospective	Paramedic students	36	102	Unknown
Mulcaster et al.[11]	2003	Prospective	Paramedic and medical students	20	438	3 attempts or significant hemodynamic or respiratory parameter alteration
Oliveira Filho et al. [10]	2002	Prospective	Anaesthesiology residents	7	895	2 attempts or appropriate for the patients' comfort or safety
Rujirojindakul et al.[18]	2014	Prospective	Paramedic students	11	388	3 attempts
Tarasi et al.[23]	2011	Prospective	Medical students	178	1627	Unknown
Toda et al.[20]	2013	Prospective	Paramedic students	32	960	2 attempts
Wang et al.[19]	2005	Retrospective	Paramedic students	891	7635	Unknown
Zhao et al.[21]	2014	Prospective	Medical students	26	194	>150 sec. within 1 attempt or desaturation

Table 1. Study characteristics No, Number of; **ETI,** endotracheal intubation; **CUSUM,** cumulative

Patients	Learning curve grouping of cases	Learning curve measures	Analysis to assess
All	Consecutive blocks of 25 ETI procedures	SR of first, second, third and more attempts	Descriptive with univariate testing of split groups
Unknown	Consecutive patients	Predicted probability of successful intubation	Univariate and multiple generalized linear regression model
General surgical	Consecutive patients	Failure rate of 20%	Standard and risk-adjusted CUSUM
Unknown	Consecutive patients	SR consecutive performed intubations	Model with a Monte Carlo procedure
Unknown	Consecutive blocks of 5 ETI procedures	Cumulative plot of SR	Descriptive with univariate testing of split groups
Unknown	Consecutive patients	SR categorised by total numbers of intubations per trainee	Descriptive
Unknown	Consecutive patients	SR categorised by total numbers of intubations per trainee	Descriptive
Unknown	Consecutive blocks of 5 ETI procedures	SR and probability of "good" intubation	Generalized linear mixed model
Excl. paediatric, cardiac and obstetric procedures	Consecutive patients	Failure rate of 20%	CUSUM
Elective surgical	Consecutive patients	Failure rate of 20%	Standard and risk-adjusted CUSUM
Unknown	Consecutive patients	Predicted probability of successful intubations	Univariate and multivariate mixed-effects logistic regression
Healthy surgical	Consecutive blocks of 3 ETI procedures	Observed intubation success and estimated probability	Univariate and multiple generalized logistic model
Unknown	Consecutive patients	Predicted probability of successful intubations	Univariate and multiple logistic regression model
Elective surgical	Consecutive patients	Consecutive SR	Descriptive

Study	Background students	No. Patients per participant (CI)	Overall SR 1st attempt per patient	Overall SR all attempts (CI) per patient	Time to intubate	Complication rate
Bernhard et al.[17]	Anaesthesiology residents	Up to 200 *(52% of the participants)*	78,70%	99,82%	-	27%
Chao et al.[22]	Medical students	9.9 (7.2 – 12.6)	-	76.8%	-	5% mucosal injury
Komatsu et al.[14]	Medical students	45 (32 – 58)	-	78%	-	-
Konrad et al.[8]	Anaesthesiology residents	90	-	-	-	-
Kopacz et al.[12]	Anaesthesiology residents	86 (73 – 99)	-	90,80%	-	-
Levitan et al.[16]	Paramedic students	7 (1 – 13)	-	46,7% (42,2-51.3%)	-	-
Levitan et al.[16]	Paramedic students	3 (0 – 6)	-	88,1% (79,6-96.5%)	-	-
Mulcaster et al.[11]	Paramedic and medical students	23 (19 - 27)	-	-	23 - 62 sec	Mucosal injury and teeth damage decreased from 24% to 0%
Oliveira Filho et al.[10]	Anaesthesiology residents	127 (81 - 173)	-	- *(Max 84,7% (3 of 7 students))*	-	-
Rujirojindakul et al.[18]	Paramedic students	35.5 (30.4 – 40.6)	-	78,40%	35 - 90 sec	No desaturation and dental trauma, otherwise unknown
Tarasi et al.[23]	Medical students	9 (6 - 12)	-	75.0% (72.9 - 77.1%)	-	-
Toda et al.[20]	Paramedic students	30	-	-	-	Mucosal injury decreased from 53% to 31% after 30 patients
Wang et al.[19]	Paramedic students	9,5 (1-74)	-	87.5% (86.7-88.2%)	-	-
Zhao et al.[21]	Medical students	3	66.70%	-	74 – 118 sec	0%

Table 2. Summary of outcome data No, Number of; **CI**, confidence interval; **SR,** success rate; **sec**, seconds.

All studies but one were performed under optimal conditions in the operation room, with the exception that the paramedic students of Wang et al. performed 17% of their intubations outside of the operation room (e.g. prehospital, emergency department, intensive care unit).[19] Also, Kopacz et al. did not state where their study was performed.[12] Half of the studies explicitly stated that no patients with expected difficult intubations were included.[10, 11, 14, 18, 20, 21] Only Bernhard et al. specifically reported that all patients were included, with no exception for expected difficult intubations and non-elective procedures.[17]

If stated, an intubation attempt was defined as the placement of a laryngoscope blade into the mouth. Only Chao et al. defined an intubation attempt as insertion of the blade in combination with an endotracheal tube.[22]

Successful ETI was defined by the registration of capnography (and auscultation) in about half of the studies. The remaining studies did not cite a definition.
Table 1 shows the analytical methods of each study. Three studies performed a CUSUM analysis to determine the minimum number of ETIs required to obtain an acceptable failure rate of 20% or less.[10, 14, 18]

Two studies also described an extra or alternative success rate. Mulcaster et al. distinguished between "successful" and "good" ETI, defining the former as the placement of an endotracheal tube into the trachea and the latter as successful intubation, including a categorisation using one subjective and 10 objective criteria. These data were incorporated into a predicted "good" ETI learning curve using a generalised linear mixed model.[11] Chao et al., Tarasi et al., Toda et al. and Wang et al. used regression models to extrapolate predicted success rates.[19, 20, 22, 23]

Data extraction

Table 2 lists the summary of outcome data per study. The number of patients per student varied from 3 to 200. The overall success rate also varied, from 46.7% (mean of 7 patients intubated per student) to 99.8% (up to 200 intubations per student, unlimited attempts).

Our own extraction of success rates of at least 80% and 90% is given in Table 3. We extracted the number of attempted ETIs per student that was required to achieve these success rates only if the statistics of the paper clearly showed this. If possible, we categorised these success rates as occurring with one, two, or all intubation attempts per patient. In Bernard et al., all of these data could be extrapolated.[17] In a number of studies, no differentiation could be made based on the number of attempts per patient. In these studies, we categorised the intubation attempts based on the total amount of permitted attempts per patient in the research protocol.[8, 11, 12, 16, 20] Other studies did not reach ≥80% or ≥90% success rates.[10, 14, 16, 18, 21-23]

As mentioned previously, three studies performed a CUSUM analysis to identify a 20% failure rate, so data could not be extrapolated to a ≥90% success rate.[10, 14, 18]

Study	Background students	Number of ETI attempts per student to reach ≥80% SR			Number of ETI attempts per student to reach ≥90% SR		
		1st attempt per patient	**1st and 2nd attempt per patient**	**All attempts per patient**	**1st attempt per patient**	**1st and 2nd attempts per patient**	**All attempts per patient**
Bernhard et al.[17]	Anaesthesiology residents	51-75	1 - 25	1 - 25	N.A.	51 - 75	51 - 75
Chao et al.[22]	Medical students	N.A.	N.A.	N.A.	N.A.	N.A.	N.A. *(28 predicted)*
Komatsu et al.[14]	Medical students	-	N.A. *(29 ETIs with 9/15 crossed 20% failure rate)*	-	-	N.A.	-
Konrad et al.[8]	Anaesthesiology residents	-	35	-	-	57	-
Kopacz et al.[12]	Anaesthesiology residents	-	-	11 - 15	-	-	41 - 45
Levitan et al.[16]	Paramedic students	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Levitan et al.[16]	Paramedic students	-	-	>1	-	-	-
Mulcaster et al.[11]	Paramedic and medical students	-	-	1-5 *(35 probability of "good" intubation)*	-	-	11-15 *(47 probability of "good" intubation))*
Oliveira Filho et al.[10]	Anaesthesiology residents	-	N.A. *(4/7 students crossed 20% failure after 43 (± 33) ETIs. 3/7 didn't cross)*	-	-	-	-
Rujirojindakul et al.[18]	Paramedic students	-	-	N.A. *(91% after 22 ETIs (18-infinity))*	-	-	-
Tarasi et al.[23]	Medical students	-	-	*(6 predicted)*	-	-	N.A. *(17 predicted)*
Toda et al.[20]	Paramedic students	-	(20 prediected)	-	-	N.A. *(32 predicted)*	-
Wang et al.[19]	Paramedic students	-	-	(3 predicted)	-	-	(16 predicted)
Zhao et al.[21]	Medical students	N.A. *(2 ETI 80% success, but 3 ETI 78%)*	-	-	N.A.	-	-

Table 3. Outcome additional analysis ETI endotracheal intubation; **SR** Success rate; **N.A.** not accomplished within study; - unable to extract data from study; **"good" intubation** see main text for explanation.

≥80% success rate

Only Bernhard et al. published results regarding a first-attempt success rate of ≥80%. Residents attempted 51–75 ETIs per student to achieve this success rate with only one attempt per patient.[17]

If more than one attempt per patient was permitted, students needed to perform 1–43 ETIs to achieve the ≥80% success rate.[8, 10-12, 14, 17, 18] Oliveira Filho and Komatsu et al. reported that about half of their students met the ≥80% success rate within two attempts per patient after respectively 26 (range 15–42) and 43 (range 9–88) ETIs. The other halves of their groups did not do better than a >20% failure rate.[10, 14]

Mulcaster et al. reported that 1–5 ETIs were sufficient for the ≥80% success rate; however, they also found that 35 attempted ETIs per student were necessary to perform a non-traumatic intubation in less than 30 seconds within 3 attempts.[8, 11]

Wang et al., Tarasi et al., and Toda et al. reported a predicted number of attempted ETIs per student to achieve a success rate of ≥80% with two or more attempts per patient. These values are 3, 6, and 20, respectively.[19, 20, 23]

≥90% success rate

The included studies did not provide much information about the number of ETIs per student to reach a first-attempt success of ≥90%. The learning curve described in Bernhard et al. indicates a need to exceed at least 200 ETI experiences.[17]

When two attempts per patient are permitted, Bernhard et al. and Konrad et al. found that 51–75 (block of 25 consecutive patients) and 57 (no range indicated) ETIs had to be attempted to reach a ≥90% success rate.[8, 17] Mulcaster et al., Kopacz et al., and Bernhard et al. showed a ≥90% success rate with any number of attempts per patient after respectively 11–15, 41–45, and 51–75 attempted ETIs (consecutive blocks of 5–25 patients, no range indicated).[11, 12, 17] Mulcaster et al., however, also reported that 47 attempted intubations per student should be performed to achieve a success rate of at least 90% for a non-traumatic intubation in less than 30 seconds.[11]

Wang et al., Tarasi et al., Chao et al., and Toda et al. reported a predicted number of attempted ETIs per student to achieve a success rate of ≥90% with two or more attempts per patient. These values are 16, 17, 28, and 32, respectively.[19, 20, 22, 23]

Complication rate

The complication rate per study is listed in Table 2. Only two studies presented data about oropharyngeal trauma in relation to the experience. Mucosal injury decreased from 53% to 31% after 30 patients in the patient group of Toda et al.[20] Mulcaster et al. reported that injury to mucosa and teeth decreased from 24% to 0% after 30 patients per student.[11]

	Bernhard et al.[17]	Chao et al.[22]	Komatsu et al.[14]	Konrad et al.[8]	Kopacz et al.[12]	Levitan et al.[16]		Mulcaster et al.[11]	Oliveira Filho et al.[10]	Rujirojindakul et al.[18]	Tarasi et al.[23]	Toda et al.[20]	Wang et al.[19]	Zhao et al.[21]
External validity														
1. Was the study's target population a close representation of the national population in relation to relevant variables?	Yes	Yes	No	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the sampling frame a true or close representation of the target population?	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was some form of random selection used to select the sample, OR was a census undertaken?	Yes	Yes	No	No	Yes	No		No	No	No	Yes	Yes	No	No
4. Was the likelihood of nonresponse bias minimal?	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Internal validity														
5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was an acceptable case definition used in the study?	No	Yes	Yes	No	Yes	No		Yes	Yes	Yes	Yes	Yes	No	Yes
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	No	No	Yes	No	No	Yes		Yes	Yes	No	No	Yes	No	Yes
8. Was the same mode of data collection used for all subjects?	Yes	Yes	Yes	Yes	Yes	No		Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Summary item on the overall risk of study bias	Mod	Mod	Mod	Mod	Low	High		Low	Low	Mod	Low	Low	High	Low

Table 4. Quality assessment

Stop criteria and possible biases

Stop criteria given by the studies varied widely. Besides stopping when the situation could be harmful for the patients, seven articles had a limit of two[8, 10, 14, 20] or three [11, 18, 22] attempts per patient. Another study used a time limit of 150 seconds.[21] The remaining articles did not mention their stop criteria.

The ratings for each article for each bias item are given in Table 4. Kopacz et al.[12], Mulcaster et al.[11], Oliveira Filho et al.[10], Tarasi et al.[23], Toda et al.[20] and Zhao et al.[21] scored as having the lowest risk of bias with this rating system whereas the publication of Levitan et al.[16] and Wang et al.[19] seemed to have the highest risk.

Discussion

This systematic review aimed to determine the number of ETIs a health care provider should perform to achieve proficiency with this procedure within two attempts per patient. Depending on the target success rate, the numbers needed to succeed in optimal elective circumstances are relatively small.

We found that after 1–43 attempted ETIs per student, most students had a ≥80% success rate within two attempts per patient.[8, 10, 14, 17, 20, 21] To increase the success rate to ≥90% within two attempts per patient, at least 50 attempted ETIs per student had to be performed in elective low-risk procedures under optimal conditions.[8, 17]

If we exclude the results of the studies with the highest risk of bias, the numbers presented above remain similar. If we only look at the studies with the lowest risk of bias, we found that after 20-43 attempted ETIs per student, most students had a ≥80% success rate within two attempts per patient.[10, 20] Within the group with low risk of bias, only Toda et al. presents data how much experience is required to reach ≥90% success rate within two attempts per patient. They predict 32 attempted ETIs per student.[20]

No clear difference existed between medical students, paramedic students or residents.

One article that was excluded from this review, Je et al., involved emergency medicine residents in training.[13] Even these trainees did not reach a ≥90% success rate in elective settings despite a mean of 114 ETIs per student. This article had to be excluded from the review because of a limited number of ETIs with videolaryngoscopy, which could lead to a higher success rate. The design, however, was similar to the included studies, implying that 50 ETIs will not be sufficient for many trainees. Furthermore, Kopacz et al. showed that maintaining a good success rate for this skill means that students sometimes need more than double the amount of ETIs.[12]

One important point to extract from Wang et al. is that the learning curves plateaued after 20–25 ETIs in the operation room and emergency department. In contrast, the learning curves in the pre-hospital setting and intensive care unit were steeper and did not plateau across a span of 30 ETIs (the learning curves were presented only for the first cumulative ETIs).[19] Similarly, the first-pass success rates of Warner's paramedic students did not plateau across the first 20 prehospital ETIs during their training.[24]

Only one of our included studies explicitly involved patients with expected difficult intubations[17] and one study explicitly included intubations in different settings[19]. Other reports mostly included elective patients in optimal circumstances in the operating room, for which the incidence of difficult intubation is 5.7–10.6%.[25-28] As stated earlier, at least 50 ETIs are needed to achieve a ≥90% success rate with this patient selection. Overall, the incidence of a difficult or failed intubation is up to 20 times higher in non-routine, non-elective settings.[3] Furthermore Cook et al. showed that the incidence of brain damage or death from an airway event is 38- to 58-fold higher in the emergency department and intensive care unit, respectively, compared with routine anaesthesia settings.[29] Even taking the different case mixes into account, these findings are astonishing and emphasise that providers who intubate in other than elective settings should be experienced airway managers. In addition to very large numbers in elective optimal circumstances, exposure in non-routine settings should be integrated into their training to optimise success rates in all settings. To maintain this skill, the Dutch health care inspectorate declared that at least 50 ETIs should be performed annually, based on expert opinion from the Dutch Society of Anaesthesiologists.[30]

Helicopter physicians performing pre-hospital ETIs are reported to intubate 84.5–87.4% at the first attempt and 96.7–98.5% at the second attempt per patient.[7, 31, 32] Paramedics have a first-attempt success rate of 46.4–77%[7, 33] and a 94%[33] success rate at the second attempt. One study with a sample size of more than 57,000 patients reported an overall paramedic ETI success rate of 86.3%.[34] In a recent study from the UK, 57% of the patients still had airway compromise when the helicopter physician arrived after a median of 16 minutes. Paramedics in that study had a 64% success rate with an unknown number of intubation attempts per patient.[35]

Unrecognised malpositioned endotracheal tubes are reported in 6–25% in the pre-hospital setting in several studies.[35-39] ETI exposure of Dutch and British paramedics is low (3–5 per year), and training programs depend on local possibilities.[40, 41] This situation has led to a widespread discussion about optimal airway manoeuvres for paramedics. A supraglottic airway device is considered a better alternative to ETI in inexperienced hands,[42-49] with success rates achieved after limited training in a short amount of time.[50-52] Another benefit is that no extra damage is done to the airway. Experts will have better chances of high first-attempt success rates when intubating. On the other hand, ventilation pressures are limited, and there is no definitive secured airway. Further and more extended research is necessary to study the effect of supraglottic airways in emergency settings regarding morbidity and mortality.

Furthermore, a success rate of 90% itself is debatable. Is a 10% failure rate acceptable when it comes to airway management with potentially devastating complications? Nowadays, procedures in health care are increasingly assessed using Motorola's concept of Six Sigma (target error rate of no more than 6 standard deviations from the process mean).[53] Obviously, this target would be impossible to achieve in this area but does raise the question of what our target should be like in an ideal situation with the most vulnerable patients. Do we need to reorganise our health care system so that the most experienced physicians encounter the most critical patients, such as trauma patients pre-hospital and ICU patients in-hospital, when necessary, 24/7?

The first limitation of this review is the small number of included studies and students per study. In addition, the four studies with the largest number of students all had a mean of less than 10 patients to intubate per student,[16, 22, 23, 54] which results in wide scatter and methodological limitations.

Second, we focussed on DL, excluding other techniques like videolaryngoscopy, and the learning curve for videolaryngoscopy might be steeper.[55-57] However, most emergency medical services are not (yet) equipped with videolaryngoscopy. Furthermore, technical and practical problems like obliteration of the view by drops of blood or secretions might limit the usability in up to 24% of prehospital intubations.[58] DL is still the gold standard technique for ETIs, and recent studies are in disagreement about whether or not videolaryngoscopy and other novel intubating aids are superior to DL.[59-65] Because the learning curve for DL might be influenced by when students are exposed to other techniques, as well, we excluded from our review studies involving any other methods.

Third, study designs differ among the publications. In some designs, an extended preliminary stage was implemented. For example, some students attended lectures, watched explanatory videos, or received mannequin training whereas other students or residents received no preliminary training.

Another limitation is the patient category included. Studies limited to paediatric patients were excluded because most providers who intubate children have experience on adults.

The last limitation is the constraint of our search results to English-language articles only. Although this is standard practice in many systematic reviews because of translation limitations, this exclusion could have led to an absence of publications in other languages that might have enhanced the robustness of the results.

Conclusions

The literature is limited regarding the learning curve for direct ETI. The conclusions made based on this literature are that under optimal elective conditions, a minimum of 50 ETIs are needed to achieve a success rate of at least 90% within two intubation attempts per patient. Because the incidence of difficult intubation in the non-elective setting is up to 20 times higher than in the elective setting, the training for pre-hospital health care providers should exceed 50 ETIs. However, the actual number or range this should be is unknown and cannot be derived from the literature we found. More research in all settings with a variety of patients and a greater number of attempted ETIs per student should be performed.

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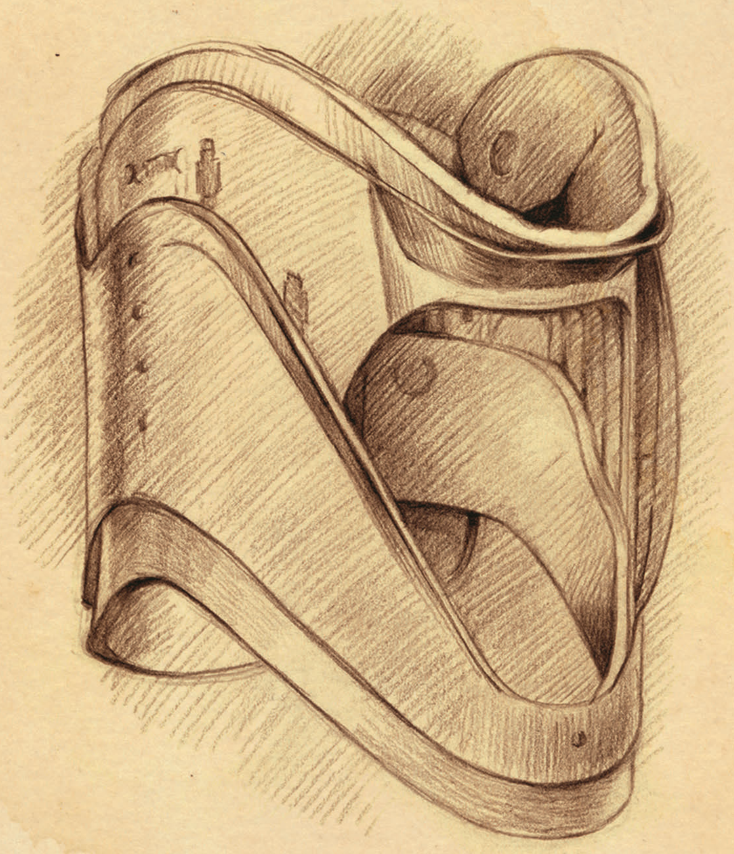
Appendix table 1; explanation per question how it was applied to our review.

Target population = health care workers who are novice intubators.
Yes = low risk of bias, No = not specified or high risk of bias
Yes = there was no specific selection on age or sex. **No** = high risk, for example only women were included.
Yes = students with a medical or paramedical background, **No** = all other students.
All participants included in a time frame (**Yes** = low risk)? If not specified or a selection was made it was defined as high risk (**No**).
Nonresponse bias was considered low risk in prospective designed studies (**Yes**) and high risk in retrospective designed studies (**No**).
Data collected directly from subjects or from supervising specialist (**Yes** = low risk, **No** = high risk).
Low risk = clear definition of a successful intubation (**Yes**), otherwise high risk (**No**).
Low risk = students data were checked by an attending supervisor (**Yes**). High risk = Not specified or not checked by a supervisor (**No**).
Not applicable.
Were correct success rates and learning curves presented? **Yes** = low risk, **No** = high risk.
Low = low risk of bias = 0-1 items classified as high risk.
Mod = Moderate risk of bias = 2-3 items classified as high risk.
High = High risk of bias = > 3 items classified as high risk.



Rigid cervical collar.

- to immobilize the neck after trauma.
- prevent from secondary spinal injuries.

Contra

- raises intracranial pressure
- some surgeons stop thinking if not applied.
- obsolete tool!

CHAPTER 7

Rise in Intracranial Pressure by application of a Rigid Cervical Collar: A pilot study in healthy volunteers

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Iscander M. Maissan, Rein Ketelaars, Boris Vlottes, Sanne E. Hoeks,
Dennis den Hartog, Robert Jan Stolker

Abstract

Objective: Rigid cervical collars are known to increase intracranial pressure (ICP) in severe traumatic brain injury (TBI). Cerebral blood flow (CBF) might decrease according to the Kellie Monroe doctrine. For this reason, the use such as the collar in patients with severe TBI has been abandoned from several trauma protocols in the Netherlands. There is no evidence on the effect of a rigid collar on ICP in patients with mild or moderate TBI or indeed patients with no TBI. As a first step we tested the effect in healthy volunteers with normal ICPs and intact autoregulation of the brain.

Methods: In this prospective blinded cross-over study, we evaluated the effect of application of a rigid cervical collar in 45 healthy volunteers by measuring their optical nerve sheath diameter (ONSD) by transocular sonography. Sonographic measurement of the ONSD behind the eye is an indirect noninvasive method to estimate ICP and pressure changes.

Results: We included 22 male and 23 female volunteers. In total 360 ONSD measurements were performed in these 45 volunteers. Application of a collar resulted in a significant increase in ONSD in both the left (Beta=0.06, 95%CI 0.05-0.07, $p<.001$) and right eye (Beta=0.01, 95%CI 0.00-0.02, $p=0.027$)

Conclusion: Application of a rigid cervical collar significantly increases the ONSD in healthy volunteers with intact cerebral autoregulation. This suggests that ICP may increase after application of a collar. In healthy volunteers, this seems to be of minor importance. Based on our findings the effect of a collar on ONSD and ICP in patients suffering mild and moderate TBI needs to be determined.

Introduction

Often, patients with head-injuries suffer from additional cervical spine injury. For decades, trauma victims have been routinely immobilized when cervical injuries could not be ruled out at the scene. Rigid cervical collars and spine boards were used during transportation in prehospital trauma care. As advocated in advanced trauma life support (ATLS) and prehospital trauma life support (PHTLS) protocols, immobilization is continued until cervical spine injury is excluded.[1,2] To minimize secondary damage to the spinal cord, in-line immobilization will be continued during transportation and examination.[3] Several devices to help immobilize the cervical spine such as the Stiffneck®(Laerdal Medical AS, Stavanger, Norway) are commercially available.

The application of rigid cervical collars increases the intracranial pressure (ICP) of brain-injured patients in ICU settings.[4-6] This rise in ICP is attributed to compression of the internal jugular veins.[7,8] According to the Kellie Monroe doctrine, impaired venous drainage causes volume expansion inside the skull, which can raise ICP and lead to neurological deterioration.[1] Besides a raised ICP, local pressure of the collar may exacerbate discomfort and agitation in patients suffering mild or moderate TBI resulting in undesirable movement of the neck and an additional rise of ICP. More information about the effects of the cervical collar on the ICP is mandatory. However, outside of the intensive care unit, it is not feasible to measure ICP directly.

Sonographic measurement of the optical nerve sheath diameter(ONSD) is a non-invasive, rapid method for indirect ICP-monitoring.[9-11] The meninges around the brain are in continuum with the optical nerve sheath, and cerebrospinal fluid percolates freely from the cranial cavity into the optical nerve sheath.[12,13] Previously, we demonstrated that any change in ICP results in a simultaneous change of the ONSD in both eyes.[9]

In this study, the effects of the application of a rigid cervical collar on the ONSD were measured in healthy volunteers. We hypothesize that a rigid cervical collar increases the ONSD (through a raised ICP) in healthy volunteers with intact cerebral autoregulation.

Methods

This blinded cross-over study was a single-center prospective research study. Volunteers were recruited in the medical library of the Erasmus University Medical Center. The volunteers were at least 18 years of age and did not have any self-reported medical history of ocular or intracranial disease. Both eyes were intact and functional. Every individual volunteer gave a written informed consent after reading the patient information form which was approved by the ethical committee of the Erasmus Medical Center, Rotterdam. (MEC-2015-460)

Rigid Collar and ONSD

ONSD was measured simultaneously in both eyes by two experienced sonographers (IM and RK) who were blinded as to whether a collar was applied to the neck or not. Both sonographers are senior e-FAST instructors since 2010 and working as helicopter emergency medical service (HEMS) physicians since 2012. Both performed over 25 ONSD examinations previous to our study. Sonographers were also blinded for each other's measurements (Figure 1A,1B).

A

B

Figure 1A. research set-up
Figure 1B. research set-up

The upper part of the volunteer's head (from the nose up) was presented to the operators through a narrow opening in the center of a room dividing screen. Between every session, the sonographer was not allowed to see the participant, while a collar was being applied or not as per randomization. All four sessions of measurements were performed with the volunteers in a supine position on a table: two with and two without application of a Stiffneck® rigid cervical collar. Measurements were performed within two minutes after application of the collar. Volunteers were instructed to breathe normally-, and not to talk or cough during the measurements. If coughing occurred, measurements were repeated. Randomization was achieved by rolling a dice in one of six "collar regimes."(Table 1)

Dice result	Session one	Session two	Session three	Session four
1	0	0	1	1
2	0	1	0	1
3	1	0	0	1
4	1	0	1	0
5	1	1	0	0
6	0	1	1	0

Table 1. Rigid Collar Regime. 0 = no collar, 1 = collar applied.

A third researcher (BV) on the other side of the screen adjusted the size of the adaptable Stiffneck® and applied it to the participants' neck as prescribed in the user manual (version and year). The cervical collar Velcro was opened and closed again before every measurement, independent of application to the volunteer's neck or not. This was done to blind the observers to audible clues as to the application or absence of the collar. During every session, heart rate, blood pressure, and blood oxygen saturation (SPO_2) were monitored noninvasively (Infinity M540, Dräger, Lübeck, Germany).

Images of the ONSD in the left and right eye were taken simultaneously with two identical M-Turbo ultrasound machines (7.5MHz linear probe; ocular setting, mechanical index = 0,2: FUJIFILM SonoSite Inc., Bothell, WA, USA). Axial measurements were carried out in B-mode. The images were frozen at the same time and ONSD's were measured by each sonographer on their machine with the internal calliper 3mm behind the retina as suggested before (Figure 2).[9-13] One sonographer measured all left eyes and the other all right eyes throughout the study.

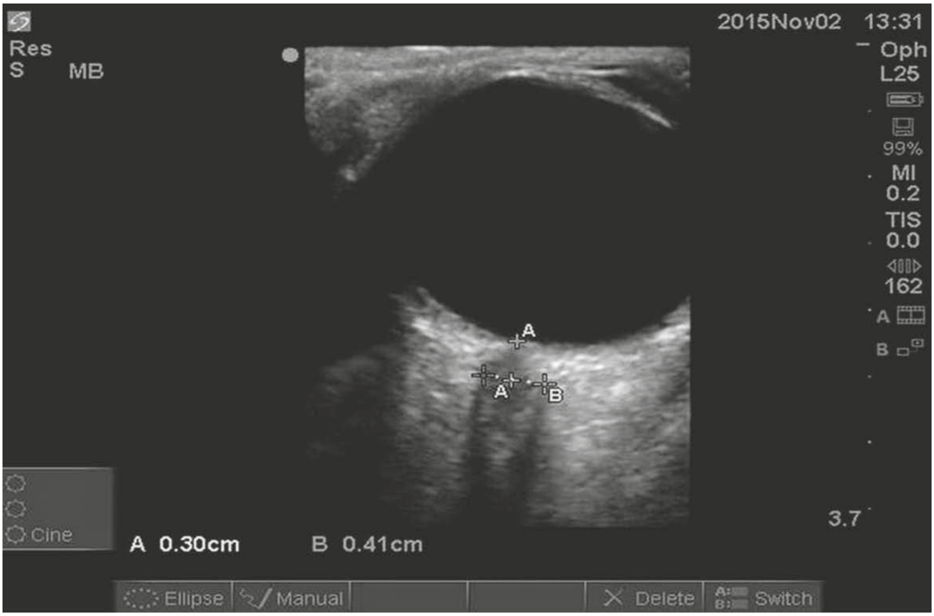

Figure 2. Sonographic image of an ONSD measured 3 mm behind the retina

Statistical analyses

Categorical variables are presented as numbers and percentages. Continuous data is presented with ranges and as mean ± standard deviation (SD) when normally distributed or as median values and corresponding 25th and 75th percentiles when data were skewed. The intra-observer variability is calculated as the mean difference between two measurements for each eye/observer with and without application of a collar and reported as mean ± SD. To evaluate the effect of a collar on ONSD, linear mixed models were fitted. This method of analysis takes into account the correlated nature of repeated measures of the same subject. The models included *volunteer* as a random factor and *collar*, *eye* and *collar by eye* as fixed within-volunteer effects. IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) and R (version 3.2.5) were used.

Results

22 male and 23 female volunteers were included. Age ranged from 18 to 31 (mean 20.3 ± 1.9) years of age. None used vasoactive medication of any kind. Systolic blood pressure (131.8 ± 8.7 mmHg), diastolic pressure (77.2 ± 5.6 mmHg), pulse (78 ± 10.8 min^{-1}), and peripheral oxygen saturation (98 ± 1 %) were within normal limits. In total, 360 ONSD measurements were performed in 45 volunteers. Intra-observer variability varied between 0.001 ± 0.05 and 0.005 ± 0.05.(Table 2)

	Range ONSD (mm)	Average ONSD (mm)	Intraobserver variability
Left eye (Observer 1)	0.38-0.78	0.54 ± 0.07	
Collar	0.40-0.78	0.57 ± 0.07	0.001± 0.05
No Collar	0.38-0.69	0.51 ± 0.06	-0.005± 0.05
Right eye (Observer 2)	0.40-0.69	0.53 ± 0.06	
Collar	0.40-0.69	0.54 ± 0.07	0.003± 0.05
No Collar	0.42-0.66	0.53 ± 0.06	0.005± 0.05
Interobserver variability (Obs1 vs Obs2)			
Collar		-0.03 ± 0.07	
No Collar		0.02 ± 0.06	

Table 2. Intra and inter observer variability

The application of the collar resulted in a significant overall increase in ONSD (5.5±0.7mm vs control 5.2±0.6, p<.001) (Figure 3). However, a significant effect of eye (left vs right) and the interaction of eye and collar was observed (Table 3). Stratification on eye revealed a rise of ONSD of 0.6mm (p<.001) in the left eye and 0.1mm (p=.027) in the right eye after application of the collar.

	Overall			Left eye			Right Eye		
	B	CI	p	B	CI	p	B	CI	p
(Intercept)	0.53	0.51 - 0.54	<.001	0.51	0.49 - 0.52	<.001	0.53	0.51 - 0.54	<.001
Collar	0.01	0.00 - 0.02	.047	0.06	0.05 - 0.07	<.001	0.01	0.00 - 0.02	.027
Left eye	-0.02	-0.03 - 0.01	.001						
Collar*Eye	0.05	0.03 - 0.07	<.001						
Observations		360			180			180	

Table 3. Estimates of linear mixed effect regression analyses on ONSD

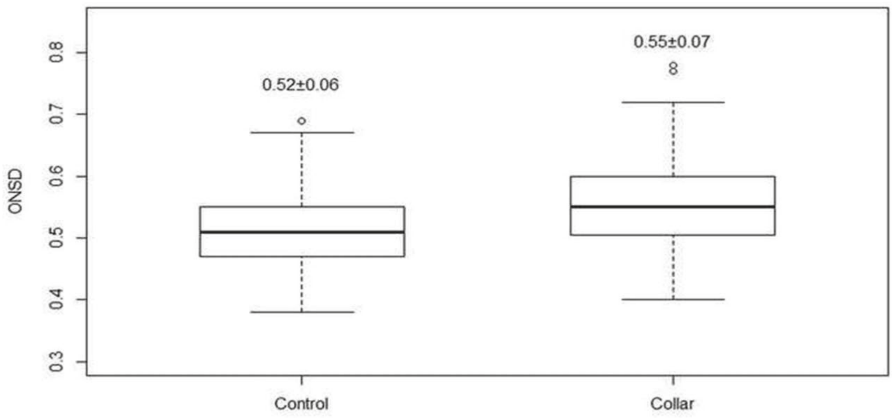

Figure 3. ONSD with and without a rigid cervical collar applied

Discussion

We demonstrated in this study that application of a rigid cervical collar in healthy volunteers results in a statistically significant increase of the ONSD. This suggests that ICP will rise when a rigid cervical collar is applied. In healthy volunteers, this is probably clinically irrelevant due to maintained cerebral blood flow (CBF) by autoregulation mechanisms. When pressure compensation mechanisms, as described by Kellie and Monroe, are exhausted, and autoregulation is impaired after traumatic injury, a rise in ICP will compromise CBF and worsen secondary brain injury.[14]

It is assumed that the ICP in healthy volunteers is equal throughout the entire cranial cavity. [1,12,13] Toscano et al. suggested no difference in ONSD distention in the left and right eye of heavily sedated and mechanically ventilated patients with increased ICP. [15] For practical reasons the positions of the sonographers were not changed during our experiment. One was seated on the left and one on the right side of the table each with their own ultrasound machine. (Figure 1A,1B)

ONSD distention due to collar application was statistically significant in both eyes but we found an unexpected difference in effect in the left and the right eye.

To our surprise the discrepancy between the left and right ONSD increased to 0.6 mm when a cervical collar was applied. This may be caused by unequal pressure effects on the neck or in the brain due to the asymmetrical design of the collar. As pressure equilibration in the head may need more time than we assumed, we might have measured too short after application of the collar (<2minutes). An asymmetrical jugular diameter might contribute to the difference found as well. [16]

Furthermore, this left-right difference might be due to a systematic measurement error (bias) between the sonographers or the ultrasound machines. However the ultrasound machines are identical.

Although both examiners used the technique as described in the method section, a structural difference in performance might have occurred due to a difference in experience of the two sonographers. One examiner (IM) has done previous research on ONSD, for the other(RK) this test was relatively new. However, the learning curve performing ONSD measurements is reported to be as short as 10 examinations for experienced physicians.[17] Both examiners had done over 25 ONSD measurements prior to this study in previous research or their work in the field. There was a structural difference in measurements of 0,2 mm between the results of the two examiners. Interobserver variability has been reported to be as little as 0.2 mm (range 0.1-0.5 mm) in experienced sonographers.[11] Measuring structures this small might introduce a standard variation due to pixel density or software limitation of the ultrasound machines. Although Sonosite machines do not have to be calibrated periodically a small difference in firmware might have introduced a systematic measurement error. (User manual Sonosite, M turbo) In future research the sonographers should regularly switch sides to prevent this type of possible bias.

As we described before, the optical nerve sheath's response to ICP depends on its elasticity. The sheath contains the fewest trabeculae three millimeters behind the retina. This explains the hyper elasticity at this part of the sheath.[12] The cut-off point for ONSD for an increased ICP (>20mmHg) is still under debate.[9,10,13,15,17,19] Goeros et al. suggest a difference in ONSD between sexes and advocates a different cut-off for males and females.[18] Maude et al. suggest possible differences between ethnicities.[20] In our previous study we found a cut-off point of 5.0 mm representing increased ICP (>20 mmHg) in sedated and intubated head-injured Dutch patients (67% males). Since sheath elasticity varies between individuals ONSD measurement is rather a qualitative than a quantitative assessment of ICP.[9,19] Because of this we can state that the increased ONSD during collar application does represent an increase of ICP but it is not possible to calculate the exact increase without knowing the elasticity coefficient of the sheath of that individual. The main question that remains, is whether or not this increase in ICP impairs CBF. If ICP compensation mechanisms described by Kellie Monroe are exhausted, the slightest increase in venous volume in the head might result in a rise in ICP and a compromised CBF.

In daily clinical practice, let alone in a prehospital setting, CBF cannot be measured easily and reliably. CBF is directly related to cerebral perfusion pressure (CPP). CPP can be calculated as the mean arterial pressure (MAP) minus the ICP.[1] When autoregulation is disturbed after trauma CPP should be kept between 60 and 70 mmHg to prevent ischemia of the brain and cardiorespiratory complications of induced hypertension.[14] The slightest compromise of venous drainage from the head after application of a rigid cervical collar might impair CBF in TBI patients and may be counterproductive whenever ICP lowering strategies are indicated.[21] In a healthy brain, cerebral autoregulation maintains CBF when systolic blood pressure fluctuates or venous blood temporarily pools in the head. In an injured brain, autoregulation might be altered or entirely dysfunctional which makes the brain vulnerable to arterial pressure fluctuations and venous stasis.[21] This possible harmful effects of the collar and local pressure pain might explain the exacerbation of discomfort and agitation we sometimes observe after application.[22]

Since 2016 Dutch prehospital trauma protocols differ from international ATLS and PHTLS protocols on the subject of cervical spine immobilization. Practise in the Netherlands is based on the evidence that the application of a rigid cervical collar increases ICP in severely brain-injured patients and the use of the collar is of questionable benefit in patients immobilised on a spine board or vacuum mattress.[4-7,24] Alternative strategies are used, such as manual in-line stabilization (MILS) during extrication and vacuum mattress, and head blocks fixed with Velcro straps to a spine board during transportation.[1,2,4-6,23,24]

Conclusion

Application of a rigid cervical collar significantly increase the ONSD in healthy volunteers with intact cerebral autoregulation. This suggests that ICP may increase after application of a collar. In healthy volunteers, the effect is limited and seems to be of minor importance. If baseline ICP is increased or autoregulation is impaired in a head injured patient, this mechanism might worsen CBF. Based on our findings the effect of the collar on ONSD and ICP in patients suffering mild and moderate TBI needs to be determined.

Acknowledgements

We would like to thank Tom Fugers from Secma inc. Vianen, The Netherlands for his unrestricted cooperation by providing two ultrasound machines and transducers for this study.

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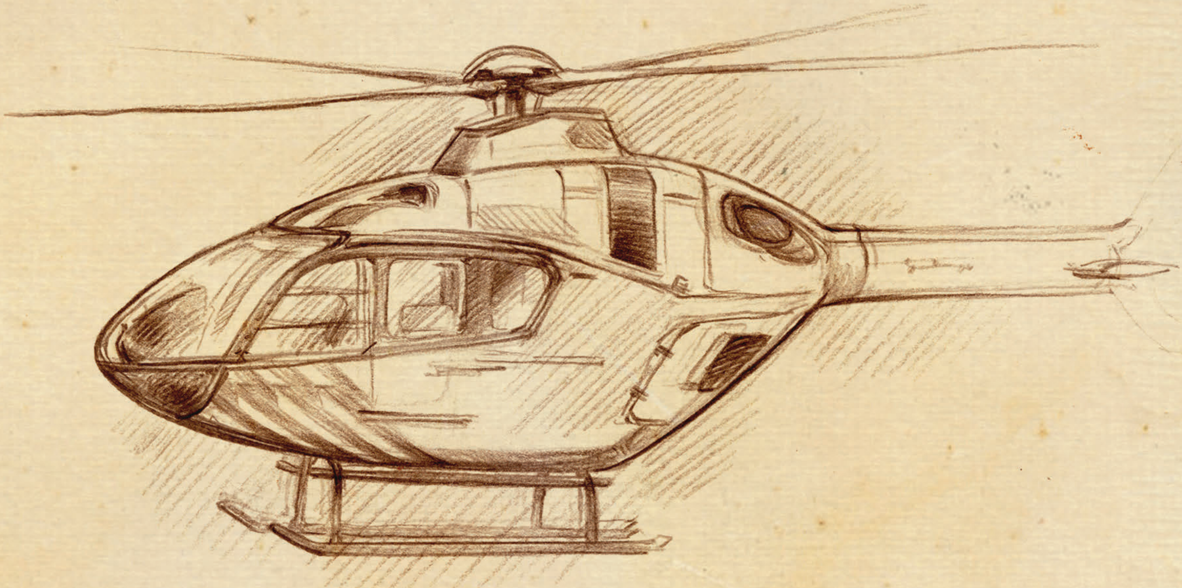
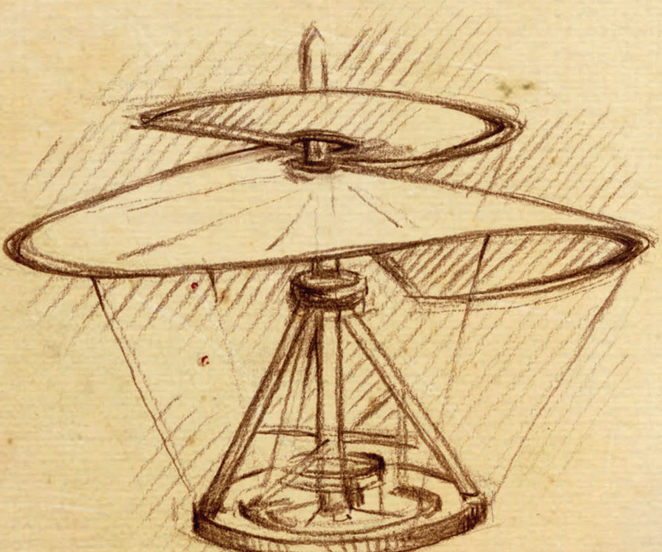


When a helicopter is in hover flight the lift of the rotordisc is equal to the weight of the helicopter.

To gain speed the rotordisc needs to be tilted forward. The horizontal component of this lift vector will increase the airspeed. In the EC-135 the fuselage attitude changes in the same direction.



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CHAPTER 8

Helicopter transportation increases intracranial pressure: A proof of principle study

Air Med J. 2018 Jul-Aug;37(4):249-252.

Maissan IM, Verbaan LA, van den Berg M, Houmes RJ, Stolker RJ, den Hartog D.

Abstract

Introduction: After severe (primary) brain injury Dutch physician based helicopter emergency medical services (HEMS) start intra cranial pressure (ICP) lowering therapy on scene to stop or delay secondary brain injury. In some cases helicopter transportation to the nearest level 1 trauma center is indicated. During transportation the head down position might counteract the ICP lowering strategies because of pooling of venous blood in the head. To exam this theory we measured the optical nerve sheath diameter (ONSD) during helicopter transport in healthy volunteers.

Methods: ONSD's were measured by ultrasound in healthy volunteers during helicopter lift off and acceleration in supine position and with a raised headrest.

Results: In this proof of principle study ONSD's increased in all volunteers during helicopter acceleration (-9° Trendelenburg; mean 5,6 ± 0,3 mm) from baseline levels (0° supine position; mean 5,0 ± 0,4 mm). After head rest elevation of the gurney (20-25°) ONSD did not rise during helicopter acceleration (mean ONSD 5,0 ± 0,5 mm).

Conclusion: Based on this study ONSD and probably ICP seems to increase during helicopter transportation in -9° head down (Trendelenburg) position. By raising the headrest of the gurney before lift-off these effects can be prevented.

Introduction

Brain injury is the leading cause of death in young adults after trauma.[1] When patients are directly transported to a level 1 trauma center to receive ICP lowering therapy as soon as possible best prognoses will be reached.[2] In 2015: one thousand and ninety two severe traumatic brain injured patients (GCS <9) were treated in the field by one of the four so called "Lifeliners" (physician staffed Helicopter Emergency Medical System) in the Netherlands. If indicated ICP lowering strategies were started on scene to optimize tissue perfusion as soon as possible and to minimize secondary brain injury.[3] (table 1)

Aim	Approach
Reduce oxygen consumption by the brain	Deep sedation
Careful intubation (high change in first pass success)	Airway expert (exposure >50/year)
Counteract vasodilatation in the skull	Controlled "normo-ventilation" ($ETCO_2$=30-35 mmHg)
Reduce brain edema	Hyperosmolar therapy
Maintain mean arterial pressure (80-100 mmHg)	Fluids and vasopressors

Table 1. Strategies used by Lifeliners in the Netherlands to reduce intracranial pressure

All patients were transported directly to a level one trauma center. One hundred and twenty three (11%) of these patients were transported by helicopter the others (89%) by car(ambulance).

Dutch Lifeliners are Airbus EC-135 type helicopters. Due to the design of the aircraft patients are positioned in the supine position, head in flight direction. The Brancard should only be used in flat position during lift-off and landing because of downward velocity criteria of the European Aviation Safety Agency.[4]

The pilot chooses a proper landing and take-off procedure depending on the characteristics of the landing location (HEMS location) Landing site should be twenty-five square meters (2 x overall length) and should be free of any obstacles. Slope should be les then 10°. Depending on the wind obstacles might block the landing or take-off track. The preferred approach is the HEMS confined profile in which the landing spot is constantly in sight during landing and take-off. (figure 1A)

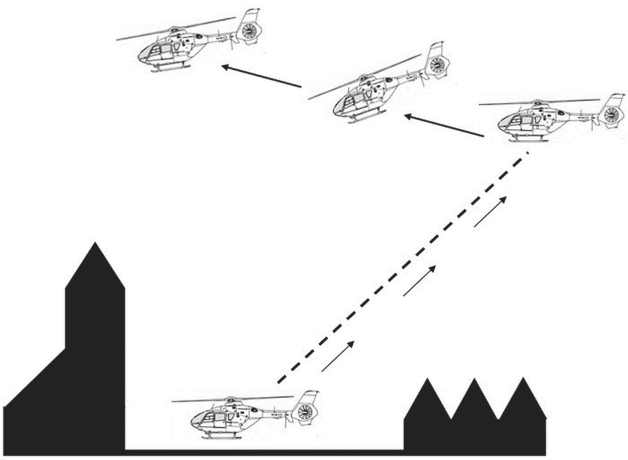

Figure 1A. HEMS confined take off

During take-off the pilot can land the helicopter back on the previous landing spot in cause of an emergency. (engine failure)

If a landing site is surrounded by high obstacles a vertical profile (figure 1B) might be suitable. If anything happens during landing or take-off, the pilot can land vertically on the spot.

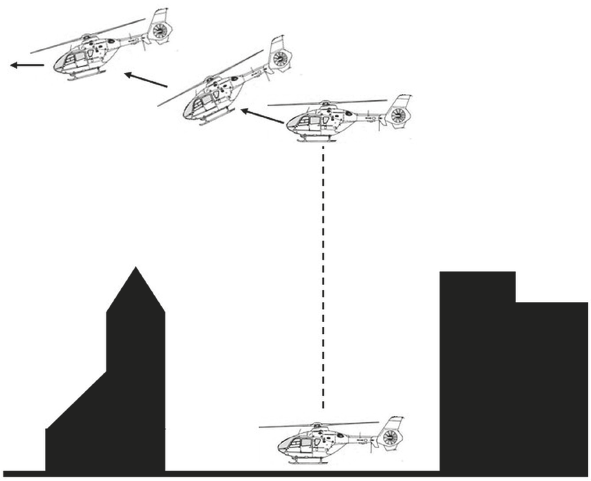

Figure 1B. Vertical take off

The patient will lay in Trendelenburg position when accelerating(-9^0) and flying(-5^0) due to helicopter flight profiles. (figure 1A,1B)

The Trendelenburg position might increase the intra cranial pressure (ICP) due to stasis of venous blood in the head.[5,6] This might counteract the ICP lowering strategies started before transportation.

We hypothesized that head-up positioning by altering the headrest of the gurney, might prevent ICP rises due to nose-down flight profile of the helicopter.[7]

To check this theory we used ultrasonic measurements of the ONSD in healthy volunteers during helicopter transportation. Previously our group and others showed that ICP changes can be measured non-invasively by measurement of the ONSD.[8,9]

Methods

This proof of principle study is conducted in accordance with the Declaration of Helsinki and complies with the principles of Good Clinical Practice (GCP). The protocol is approved by the Medical Ethics Committee (METC) of Erasmus Medical Center Rotterdam. (MEC-2016-409)

Volunteers are scouted at the medical faculty and baseline measurements of the ONSD are taken in the recovery room of our operation department to evaluate the volunteers on their echogenicity (Benchmark-baseline measurements)

The next day volunteers are placed in a EC-135 type helicopter in supine position. ONSD's are measured during lift-off (0°) and acceleration (- 9°). (Figure 2) The third measurement is taken during acceleration with the head rest elevated. In our experiment we elevated the headrest 20 – 25° due to brancard characteristics.

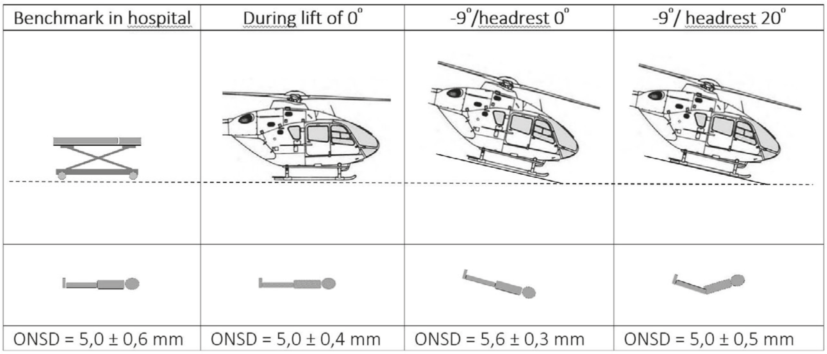

Figure 2. The four measurements performed

ONSD's of the right eyes were visualized in an axial plane (figure 3A) and measured 3 mm behind the retina (figure 3B) as described in previous literature. [5,6,8-12]

Basic vital parameters (blood pressure, pulse and saturation) are monitored during these measurements. All measurements are taken on the same flight height (500 ft) except for the benchmark – baseline measurement in the hospital.

Inclusion and Exclusion criteria

Healthy adults (≥ 18 years) with no self-reported medical history of ocular or brain disease.

Figure 3A. Axial plane measurement of the right ONSD during flight

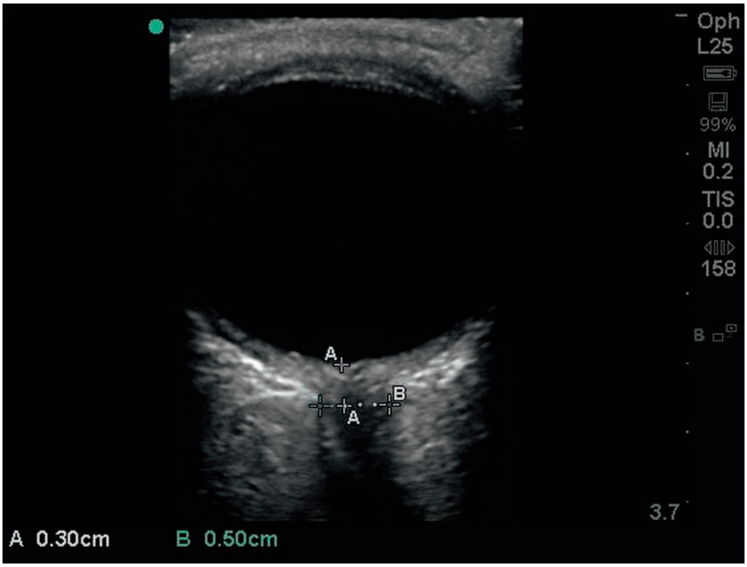

Figure 3B. ONSD measurement 3 mm behind the right eye

Results

We included three males and two females. Basic parameters (blood pressure, pulse and saturation) were considered normal. An increase in ONSD during acceleration (- 9^0) and decrease to baseline in ONSD after gurney correction was seen in all volunteers. (table 2)

Subject					
	1	**2**	**3**	**4**	**5**
Sex	M	F	M	F	M
Age (years)	21	22	25	22	24
Weight (kg)	60	60	68	58	85
Holding ONSD (cm)	0.55	0.51	0.44	0.39	0.55
Baseline helicopter ONSD (cm)	0.42	0.40	0.50	0.44	0.67
9° incline helicopter ONSD (cm)	0.56	0.53	0.56	0.51	0.64
25° gurney correction ONSD (cm)	0.46	0.50	0.51	0.42	0.60
Average blood pressure (mmHg)	112/68	108/69	123/72	115/66	151/83
Average oxygen saturation (%)	98	98	98	98	98

Table 2. Characteristics of the five subjecs
M, male; F, female; ONSD, optical nerve sheath diameter.

The overall mean baseline ONSD during our screening measurements in the hospital was 5,0 ± 0,6 mm. The overall mean baseline ONSD in the helicopter while hovering (0°) was 5,0 ± 0.4 mm and 5,6 ± 0.5 mm during helicopter incline (-9°). The overall mean ONSD after gurney correction was 5,0 ± 0.5 mm. As can be seen in figure 2 , the overall mean ONSD follows the expected pattern of increased ONSD during helicopter incline and normalization after gurney correction.

Discussion

This experiment suggests that helicopter transportation might impair brain perfusion in patients suffering TBI. After initiating ICP lowering strategies on scene, helicopter transportation might counteract the beneficial effects due to the inflight Trendelenburg position.[6] When a helicopter is in hover flight the lift of the rotordisc is equal to the weight of the helicopter. To gain speed the rotordisc needs to be tilted forward. The horizontal component of this lift vector will increase the airspeed. In the EC-135 the fuselage attitude changes in the same direction. Raising the headrest of the gurney before lift-off might compensates for this effect.

The user's manual of the helicopter prescribe strict rules of passenger fixation and gurney position during lift off and landing. We suggest to reconsider these regulations because of the negative effect of Trendelenburg position on the ONSD. Increases in OSND in Trendelenburg position has been suggested in the literature before.[5,6]

The optical nerve sheath (ONS) is in continuum with the meninges that surround the intracranial cavitus.[10,11,13] Hereby the optic nerve sheath is subjected to the same pressure changes as the intracranial compartment.[7,13,14] Raised ICP results in a distention of the ONS that can be measured by transocular ultrasound. We performed axial measurements 3 mm behind the retina as described before in literature.[8,9] To date, several studies investigated the relationship between the ONSD and ICP with high sensitivity of 0.90 (95% confidence interval 0.80-0.95) and a specificity of 0.85 (95% confidence interval 0.73-0.93).[15] The correlation between ICP and ONSD during acute changes in ICP is considered high(R^2=0.80).[8]

ONSD measurement does have its limitations. Sheath elasticity seems to vary between individuals making it a rather more qualitative than a quantitative assessment of ICP.[8,9] It is useful as a trend monitor when evaluating ICP changes due to interventions.[8] So we can state that the increased ONSD during helicopter transportation does represent an increase of ICP but it is not possible to calculate the exact increase. Based on our previous work we can conclude that decreased ONSD after adjustment of the head rest of the gurney does represent a lower ICP in our volunteers.[8]

In patients suffering severe head injury the hemodynamic autoregulation of the brain might be impaired or even be absent. This makes the brain more vulnerable to venous stasis and changes in blood pressure and ICP.[1] Secondary brain injury will occur wh

Conclusion

Based on this study ONSD and thereby ICP seems to increase during helicopter transportation in head down (-9° Trendelenburg) position. By raising the headrest of the gurney before take-off these effects can be prevented although the risk of spinal cord lesions may be increased.

Acknowledgements

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We would like to thank Tom Fugers from Secma inc. Vianen, The Netherlands for his unrestricted cooperation by providing two ultrasound machines and transducers for this study.

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We demonstrate that ultrasonografic ONSD measurement is highly correlated with direct ICP changes.

In ICU settings, invasive, continuous ICP measurement with intra cranial pressure probes remains superior to this non-invasive, intermittet ONSD ultrasonography because it delivers continous values.

CHAPTER 9

Ambulance deceleration causes increased intra cranial pressure in supine position: A prospective observational proof of principle study

Scand J Trauma Resusc Emerg Med. 2021 Jun 30;29(1):87.

Iscander Michael Maissan, Boris Vlottes, Sanne Hoeks, Jan Bosch,
Robert Jan Stolker, Dennis den Hartog.

Abstract

Background: Ambulance drivers in the Netherlands are trained to drive as fluent as possible when transporting a head injured patient to the hospital. Acceleration and deceleration have the potential to create pressure changes in the head that may worsen outcome. Although the idea of fluid shift during braking causing intra cranial pressure (ICP) to rise is widely accepted, it lacks any scientific evidence. In this study we evaluated the effects of driving and deceleration during ambulance transportation on the intra cranial pressure in supine position and 30° upright position.

Methods: Participants were placed on the ambulance gurney in supine position. During driving and braking the optical nerve sheath diameter(ONSD) was measured with ultrasound. Because cerebro spinal fluid percolates in the optical nerve sheath when ICP rises, the diameter of this sheath will distend if ICP rises during braking of the ambulance. The same measurements were taking with the headrest in 30° upright position.

Results: Mean ONSD in 20 subjects in supine position increased from 4.80 (IQR 4.80 – 5.00) mm during normal transportation to 6.00 (IQR 5.75 – 6.40) mm ($p < 0.001$) during braking. ONSD's increased in all subjects in supine position.

After raising the headrest of the gurney 30° mean ONSD increased from 4.80 (IQR 4.67 – 5.02) mm during normal transportation to 4.90 (IQR 4.80 – 5.02) mm ($p = 0.022$) during braking. In 15 subjects (75%) there was no change in ONSD at all.

Conclusions: ONSD and thereby ICP increases during deceleration of a transporting vehicle in participants in supine position. Raising the headrest of the gurney to 30 degrees reduces the effect of breaking on ICP.

Background

Traumatic brain injury(TBI) is the leading causes of death in young people.[1] It's incidence is 262/100.000 people and is responsible for 10.5 deaths per 100.000 inhabitants in Europe.[2] After primary brain injury occurs, hypo-perfusion of the brain and low oxygen saturation of the blood can cause secondary brain injury.[3] Hypo-perfusion of brain tissue can be caused by low systemic blood pressure, but more often by an increased intracranial pressure (ICP) that compromises cerebral blood flow[3,4]. Cerebral perfusion pressure(CPP) is defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). There is a relationship between the time of low CPP's and the extent of secondary brain injury.[5] Autoregulation of cerebral perfusion is often impaired or absent after head injury which makes the brain more vulnerable to pressure changes.[3,4] An increase in ICP during an ambulance ride could compromise cerebral perfusion and induce ischemia of the brain, further increasing the risk of secondary brain injury.[3]

In the Dutch prehospital care system ambulances are manned by a medically trained driver and a specialized nurse that can provide advanced life support to most patients and circumstances. Physician staffed mobile medical teams can be dispatched to assist ambulance crews in high complex cases. When traumatic brain injury has occurred these teams are utilized to start anaesthetic brain protective therapy in the field. Anaesthesia decreases the oxygen consumption of the brain and lowers the ICP.[6] Hypertonic saline may decrease brain tissue swelling and elevating the headrest results in better drainage of venous blood from the head trough gravitational forces.[7-9] Head-injured patients should primarily be admitted to a level 1 trauma center for better neurological outcomes.[5] These level 1 trauma centres are widespread across the country and may therefore lead to longer transportation times. Based on the hypothesis that fluid shifts increases ICP ambulance drivers in Netherlands are trained to drive as smoothly as possible.[10,11] The hypothesis states that fluid shifts have the potential to increase the ICP during deceleration of the moving ambulance due to increased venous stasis and backflow in the head. A similar mechanism has been proven to increase the ICP and optical nerve sheath diameter (ONSD) in Trendelenburg position and after application of a rigid cervical collar.[12,13]

The ONSD is in continuum with the intracranial cavity and cerebro spinal fluid percolates freely in the optical nerve sheath. When the ICP rises the diameter of this sheath will distend.[14,15] To our knowledge there is no scientific evidence on the effects of deceleration on the ICP in trauma patients. The objective of this study is to examine this in healthy subjects with sonographic ONSD measurement. We hypothesize that raising the headrest of the gurney 30° upwards will decrease ICP during deceleration. The aim of the study is to provide knowledge on how to safer transport TBI patients.

Methods

This observational study was set up as a prospective proof of principle study. Twenty participants were recruited from the regional ambulance service Hollands Midden. The participants were aged over 17 years and didn't have any self-reported ocular, intracranial disease or vaso-active medication. The medical ethical commission of the Erasmus Medical Center in Rotterdam waived a full review according to the Dutch Medical Research with Human Subjects Law. (MEC2018-1377) All participants were employees of the ambulance service and responded to a written invitation on the intranet of the company and gave their written informed consent.

The experiment was carried out on all participants on the 9th of July 2019 between 8:00 am and 5:00 pm.

To perform measurements during ambulance driving we used a regular ambulance (Mercedes Sprinter 419 cdi bluetec. 190 PK, Stuttgart, Germany) in which participants were transported in head first supine position on a gurney. Participants were axially fixated with a Kendrick Extrication Device (KED from Ferno-Washington Inc. Ohio, USA). They were placed in supine position inside the ambulance and were fitted with a bicycle helmet which contained two mounts. (figure1a,1b)

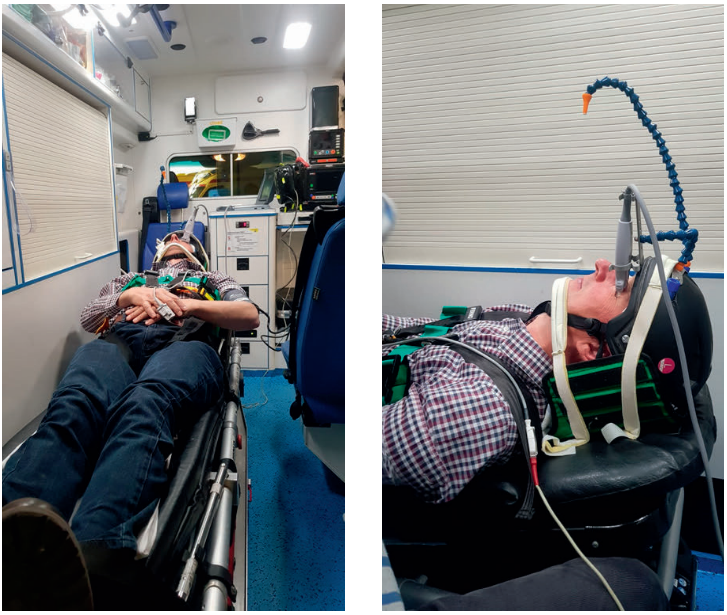

Figure 1a 1b. Research setup in the back of the ambulance with the two mounts on the helmet. One to hold the transducer and the other to create a focus point for the non-measured eye to prevent from moving the eyes during braking.

The helmet was adjustable to account for different sizes of head circumference. (58-61 cm / 22 ¾ - 24 inch). The first mount held the probe of the ultrasound machine (M-Turbo with 7.5MHz linear probe; ocular setting, mechanical index = 0.2: FUJIFILM SonoSite Inc., Bothell, Washington, USA). This mount made it possible to visualize and freeze the picture of the ONSD during deceleration and measure the diameter direct afterwards. The second mount held an extended arm with an orange dot at the end for the contralateral eye to focus on during deceleration. The helmet was fixated to the KED as a non-slidable whole to prevent the helmet from moving on the head during deceleration. Both the helmet and the KED were applied to the volunteer as described in the user's manual of the devices.

A baseline ONSD measurement without acceleration and deceleration was performed for all participants. For the second measurement the ambulance steadily accelerated to a speed of 50 kilometres per hour (km/h) and subsequently decelerated to a speed of 0 km/h on a 10 meter distance track. During deceleration the freeze button was pressed and the ONSD was measured with the ultrasound probe on the left eye by an experienced sonographer[IM]. The examiner was seated at the ambulance chair on the head side of the gurney. The third and fourth measurements were conducted in identical approach, however with the headrest of the gurney raised 30° upwards. A digital leveller was used the measure the angle.(Bubble Level PRO by Gamma Play on an Samsung Galaxy S8 Android Device) All participants had their blood pressure, pulse rate and oxygen saturation measured during the experiment with the standard ambulance monitor (Tempus ALS, RDT/Philips Healthcare, Amsterdam, The Netherlands).

For this experiment the ambulance was driven by an experienced well trained ambulance driver. All experiments were taken on the same driving school training circuit. (Bremmer transportcollege, Hazerswoude, the Netherlands)

Participant characteristics are described as number (percentage) or mean (standard deviation) / median (interquartile range). Normal distribution of the data was assessed by visual inspection of histogram and Q-Q plots and/or normality test. Difference in ONSD between the conditions were analysed using the Wilcoxon signed-rank test because results were not normally distributed. We considered the ONSD to be clinically relevant changed if the ONSD differed > 0,2mm from the baseline measurement since the intra-observer variability has been reported to be 0.2mm in previous literature.[14]

Results

We included 20 healthy participants after they had given their written informed consent. Participant characteristics are shown in table 1.

Variable	Value (SD)
No. of subjects	20
age in years	40 (10)
No. of males (%)	15 (75%)
Baseline oxygen saturation	97 (1)
Post-test oxygen saturation	96 (1)
Baseline systolic blood pressure	132 (10)
Post-test systolic blood pressure	132 (10)
Baseline diastolic blood pressure	81 (10)
Post-test diastolic blood pressure	82 (11)
Baseline heart rate	71 (10)
Post-test heart rate	71 (8)

Table 1. participant characteristics

Vital parameters such as systolic blood pressure, diastolic blood pressure, pulse and pulse oximetry were all considered in normal range both before and after testing. The ONSD measurements are shown in figure 2.

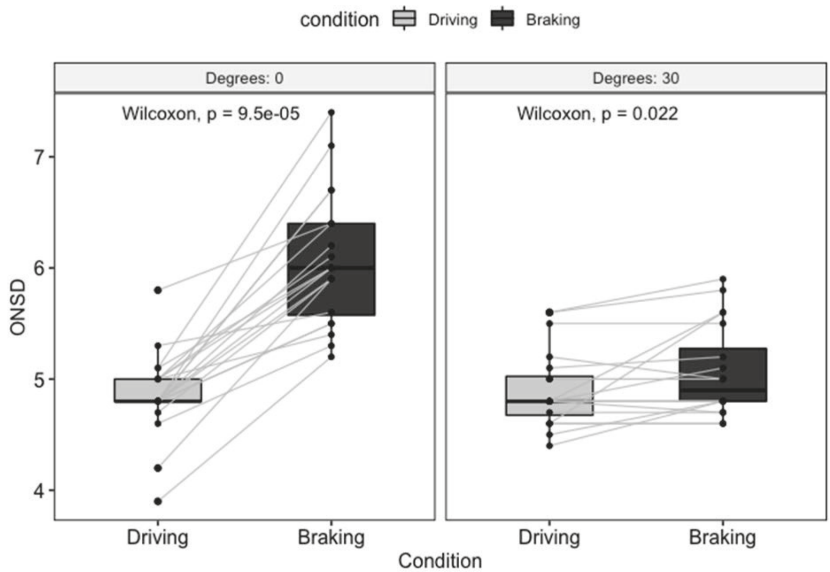

Figure 2. ONSD during driving and braking of the ambulance in 0 degrees and 30 degrees head up position

With the gurney at 0 degrees the ONSD during baseline and braking measurements was 4.80 (IQR 4.80 – 5.00) mm and 6.00 (IQR 5.75 – 6.40) mm respectively ($p < 0.001$). Raising the gurney to 30 degrees resulted in an ONSD baseline and during braking measurements of 4.80 (IQR 4.67 – 5.02) mm and 4.90 (IQR 4.80 – 5.02) mm respectively ($p = 0.022$). Overall, a 24% increase in ONSD during braking with the gurney at 0 degrees and a 0% increase in ONSD during braking with the gurney at 30 degrees was observed. All 20 participants with the gurney at 0 degrees showed > 0.2mm increase in ONSD during braking, whilst with the gurney at 30 degrees 5 participants showed > 0.2mm increase in ONSD during braking.

Discussion

In this study we investigated the relationship between the fluid shifts during ambulance braking and ICP increases. The results demonstrate that the deceleration force of braking increases the ONSD and hence rises ICP during ambulance transportation in supine position.

Elevation of the headrest (30 degrees) is part of the ICU protocol for patients with persisting elevated ICP's (> 20 mmHg) to drain superfluous venous blood from the head.[5]

Today's prehospital transportation protocols in the Netherlands prescribe immobilisation in supine position.[9,10] Based on our results we may reduce secondary brain injury by raising the headrest as soon as possible in pre hospital care if systemic blood pressure is in normal or supra-physiological range. One can argue that raising the headrest may worsen neurological outcome of the lower extremities if lumbar spinal injury is present. Although there is a risk of iatrogenic paralyzes of the legs we consider life should be treated before limb if severe TBI is suspected. To evaluate the effects of an elevated headrest on ONSD changes in a decelerating ambulance we used ultrasound to measure the sheath that surrounds the optical nerve behind the eye. This sheath is in a continuum with the meninges around the brain. Cerebro-spinal fluid percolates freely from the intra cranial cavitum into the sheath. This results in a sheath distention when the intra cranial pressure rises.[15] This method has shown a reliable diagnostic accuracy (sensitivity 0.90 [CI 0.80 – 0.95,] specificity 0.85 [CI 0.73 – 0.93]) for detecting a raised intracranial pressure.[16,17] Previously our group reported that sonographic measurement of the ONSD can be used as a quick and non-invasive monitor of changes in intracranial pressure in one individual (R^2 = 0,80).[14] In this study we took several measurements in different circumstances in the same volunteer including a baseline measurement to evaluate possible changes in ONSD during transportation. Although the correlation between ICP and ONSD seems to be strong in repetitive measurements the clinical consequences aren't clear. ONSD response to pressure changes seems to be a linear correlation but depends strongly on the elasticity of ones sheath.[15] Differences in baseline ONSD's have been reported in different sexes and ethnic groups.[18] The cut-off point of the ONSD representing ICP ≥ 20 mmHg is still under debate. This means that we can't calculate ICP's from ONSD's and we should considered the ONSD's to be rather qualitative than quantitative data.[14]

Although our testing setup is as much standardized as it could get, the forces may have been slightly different in the repeated deceleration measurements.

Because measurements were taken during transportation the examiner could not be blinded to the intervention of braking. This may have introduced an observer bias in this study. Although we think fluid shift leads to an increase in ICP and ONSD it may as well be increased due to anxiety and breath holding during braking.[219] This effect seems to minor as in upright position the increase in ICP is diminished largely but can explain the significant rise in ONSD in elevated position.

After traumatic brain injury has occurred time is of the essence to prevent secondary brain injury to extend and worsen patient outcome. Based on the findings in this experiment we suggest to revise the current transportation protocols and elevate the headrest of the ambulance gurney as soon as feasible when transporting brain injured patients.

Conclusions

ONSD and thereby ICP increases during deceleration of an transporting vehicle in patients in supine position. Raising the headrest of the gurney to 30 degrees reduces the effect of breaking on ICP. More research is needed on this subject with varying driving speeds, varying headrest angles and eventually with actual TBI patients during transportation.

Acknowledgements

We thank Bremmer transportcollege for their hospitality, RAV Hollands Midden for the use of their ambulance and equipments, Gert Jan Stuurman and Marco Gaastra for their constant driving skills, Marcel Durieux for the prior preparations and support on the day of the experiments, Willem van 't Leven for designing and manufacturing the mounts on the helmet.

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CHAPTER 10

Observer variability as a determinant of measurement error of ultrasonographic measurements of the optic nerve sheath diameter: a Systematic Review

Journal of Emergency Medicine 2022 Aug;63(2):200-211.

Rutger Hollestelle, Daniël Hansen, Sanne Hoeks, Nico van Meeteren,
Robert Jan Stolker, Iscander M. Maissan.

Abstract

Background: Ultrasonographic measurements of the diameter of the sheath of the optic nerve can be used to assess intracranial pressure indirectly. These measurements come with measurement error.

Objective: To estimate observers' measurement error as a determinant of ultrasonographic measurement variability of the optic nerve sheath diameter.

Methods: A systematic search of the literature was conducted in Embase, Medline, Web of Science, the Cochrane Central Register of Trials and the first 200 articles of Google Scholar up to April 19 2021. Inclusion criteria were: healthy adults, B-mode ultrasonography and measurements 3 millimeters behind the retina. Studies were excluded if standard error of measurement could not be calculated. Nine studies featuring 389 participants (median = 40; range 15-100) and 22 observers (median = 2, range 1-4) were included**.** Standard error of measurement and minimal detectable differences were calculated to quantify observer variability. Quality and risk of bias were assessed with the Guidelines for Reporting Reliability and Agreement Studies.

Results: The standard error of measurement of the intra- and inter-observer variability had a range of 0.10 – 0.41 mm and 0.14 – 0.42 mm, respectively. Minimal detectable difference of a single observer was 0.28 – 1.1 mm. Minimal detectable difference of multiple observers (range 2 - 4) was 0.40 – 1.1 mm. Quality assessment showed room for methodological improvement of included studies.

Conclusion; The standard errors of measurement and minimal detectable differences of ultrasonographic measurements of the ONSD found in this review with healthy participants urge caution interpreting results acquired with this measurement method in clinical context.

Introduction

Globally 5.48 million people suffer from severe traumatic brain injury each year.[1] The life expectancy of survivors of traumatic brain injury is up to 60% lower than that of the general population.[2] One of the main challenges traumatic brain injury poses is elevated intracranial pressure (ICP), as it may compromise cerebral blood flow.[3,4] Eventually this leads to secondary brain injury

So far, the gold standard of measuring ICP is through invasive devices, like an intraparenchymal probe or extra-ventricular drain.[5,6] Such a time consuming procedure is not always feasible or available, e.g. during prehospital trauma care or in most emergency departments. An indirect way to evaluate the ICP is through ultrasonographic measurement of the optic nerve sheath diameter (ONSD). This is a quick, non-invasive method to evaluate the ICP, requiring nothing but an ultrasound device and an experienced observer. The average ONSD in a healthy, adult population is 4.78 mm (95% CI 4.63 – 4.94) as measured with transorbital sonography, with no significant differences regarding gender or geographic region.[7]

Several meta-analyses tried to find a universal cut-off value of the ONSD for a pathologically increased ICP.[8-11] Since definitive cut-off points are still under debate, differentiating between a physiological and pathological ONSD is challenging. Nevertheless, the ONSD can be used to evaluate the trend of the ICP in an individual patient.

Fluctuations in ICP immediately affect the ONSD.[12] In order to evaluate a trend over time it's crucial to know whether a measured difference is an actual difference due to (patho)physiological changes or an artifact due to measurement error.

Every measurement comes with measurement error, stemming from the apparatus, the measurement technique, the observer, the context and circumstances under what the measurement was executed or combinations of these determinants. This causes repeated measurements in a stable subject to differ, as repeated measurements will vary around the "true" value.[13] As observer variability is one of the determinants that may affect the outcome of measurements, it should be accounted for when interpreting results.

Measurement error can be quantified with the standard error of measurement (SEM). SEM is a suitable parameter to assess observer variability.[14] The SEM offers two distinct advantages. Firstly, the minimal detectable difference (MDD) is derived from the SEM.[15] This is the smallest difference that exceeds measurement error. The MDD is necessary to monitor the ONSD over time. That, in turn, can be used to detect any deterioration of the ICP, or evaluate the effect of an intervention targeting the ICP. Secondly, it's possible to construct a 95%-CI around an index measurement using the SEM.[14] One can be 95% certain the 'true' value of the index measurement lies in between those limits. This information is a prerequisite if the ONSD is to be used as a screening tool, e.g. during primary survey in the emergency department.

The aim of this systematic review is to estimate observers' measurement error as a determinant of ultrasonographic measurement variability of the optic nerve sheath diameter in adults without signs of elevated intracranial pressure.

Methods

Search methods

The reporting of this systematic review was guided by the standards of the PRISMA statement.[16] A systematic search strategy was used for the following databases; Embase, Medline, Web of Science, the Cochrane Central Register of Trials and the first 200 relevant articles of Google Scholar.[17] The search strategy consisted of terms related to 'optic nerve sheath diameter,' and 'ultrasonography.' The complete search strategy is presented in Online Appendix A.[18] The first search was conducted the 13th of October 2020. The search was repeated the 19th of April 2021. This review was not registered in PROSPERO.

Inclusion criteria

Two authors (RH and DH) independently screened title and abstract for eligibility. The following inclusion criteria were used: 1. An adult (sub)population of healthy participants, without signs of increased ICP, 2. the use of B-mode ultrasonography to determine the ONSD, 3. ONSD measurements performed 3mm behind the retina and 4. any mentioning of intra- or interobserver variability. The articles that met these criteria had their full text reviewed. Articles were excluded if they did not contain enough information to calculate the SEM. Either standard deviations of repeated measurements in combination with a reliability coefficient had to be provided, or Bland and Altman's 'limits of agreement" (LoA) method. Calculation of the SEM is further explained below.

When ONSD measurements were performed on both healthy volunteers and on patients with increased ICP, data of observer variability had to be provided separately for both groups. Any review disagreement on inclusion of articles was solved through discussion between the two reviewers, and, when necessary the last author (IM).

Data extraction

The following data was extracted: year and country where the study is performed, number and characteristics of study participants, number and experience of observers, which transducer was used, how the ONSD was defined, method of consecutive measurements (e.g. new measurements vs. offline reassessment of previously recorded images), measurement conditions, the interval between consecutive measurements of the ONSD, which axis and technique was used to measure ONSD, and methods used to assess intra- and inter-observer variability.

Finally, the data required to calculate SEM were extracted per eye, i.e. standard deviations of ONSD measurements per observer and corresponding reliability coefficients, or standard deviations of the difference from Bland and Altmans' LoA method.

Quality assessment

Both reviewers (RH and DH) independently assessed the quality of the included articles using the guideline proposed by Kottner et al.[19] This guideline suggests 15 points that should be addressed in reliability and agreement studies. We provided the scores with motivation and connotations. Any disagreement was solved through discussion between RH and DH.

The standard error of measurement

If the SEM was not provided, SEM was calculated using the following formula(20):

$$SEM = SD * \sqrt{1 - R_x}. \qquad \textit{Equation 1}$$

SEM = Standard error of measurement
SD = Standard deviation
R_x = Reliability coefficient

Both Intraclass Correlation Coefficients (ICC) and Pearson's R are viable as reliability coefficient, though Pearson's R is less accurate.[20] Cronbach's Alpha (CA) is an ICC, i.e. $ICC_{consistencty}$

To calculate the SEM of inter-observer variability (SEM_{inter}) it's necessary to calculate a pooled standard deviation using

$$SD_{pooled} = \sqrt{\frac{SD_1^2 + SD_2^2 + \cdots + SD_k^2}{k}}. \qquad \textit{Equation 2}$$

If Bland and Altmans' LoA was used, the SEM can be calculated by dividing the standard deviation of the differences by √2.[15]

The minimal detectable difference (MDD) is calculated as(14)

$$MDC = 1.96 * \sqrt{2} * SEM. \quad \textit{Equation 3}$$

SEM and MDD are calculated in absolute values. MDD is also calculated in percentages of the corresponding ONSD.

Results

We identified 1004 potential articles. 32 of these articles underwent full text review. Nine articles with 389 subjects (median = 40, range 15-100) and 22 observers (median = 2, range 1-4) fulfilled the in- and exclusion criteria and were included in the assessment. The inclusion and exclusion process is summarized in Figure 1. Study characteristics are displayed in Table 1.

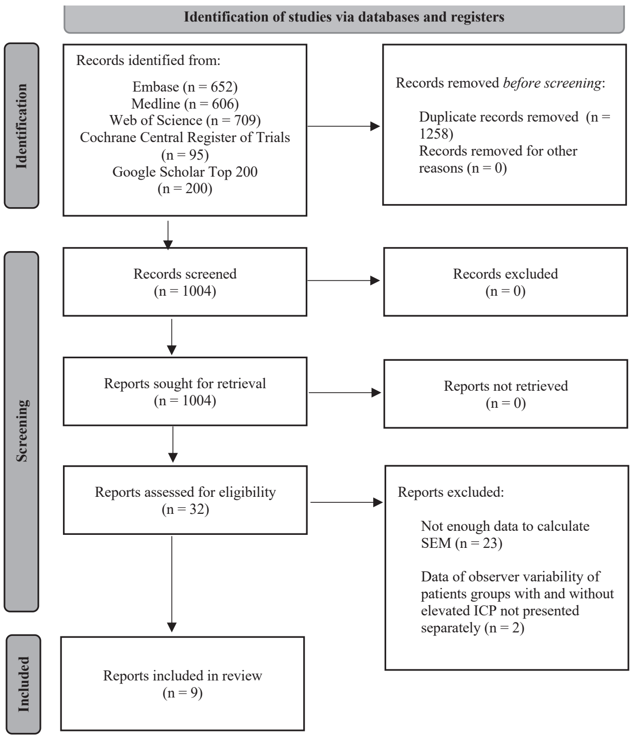

Figure 1. Flowchart of study selection and inclusion. Adapted from the PRISMA statement 2020 (16)

Study	Year	Country	N_p (%male)	Mean Age	N_O	E_O	Setting	MRM	TBM	Technique	Ultrasound	R_x intra-observer	R_x inter-observer
Amini et al.(29)	2015	USA	42 (52%)	24	2	n.c.	LC	SR	Same session	Axial Coronal	Sparq 10-5 MHz	ICC	n.a.
Asghar et al.(21)	2015	Pakistan	100 (59%)	31.1	1	n.c.	LC	SR	Same session	Longitudinal	Mindray 7.5 MHz	ICC	n.a.
Bäuerle et al.(22)	2012	Germany	40 (37.5%)	37.9	2	n.c.	LC	SR	Same session	Longitudinal	Philips iU22 9-3 MHz	CA	LoA
Bäuerle et al.(23)	2013	Germany	15 (33.3%)	24.5	2	n.c.	LC	SR + ORA	Same session/ 60-86 days	Longitudinal	Aplio XG 4-11 MHz	LoA	LoA
Lochner et al.(24)	2016	Italy	20 (35%)	46.3	2	n.c.	LC	SR	Same session	Longitudinal	Mindray 10 MHZ	CA	LoA
Maissan et al.(25)	2018	Netherlands	45 (48.9%)	20.3	2	> 25 ONSD scans	LC	SR	Same session	Longitudinal	M-Turbo 7.5 MHz	LoA	LoA
Ozturk et al.(27)	2015	Turkey	60 (n.a.)	n.a.	4	> 25 ONSD scans	LC	SR	7 days	Axial Axial in sagittal plane	Mindray 10 MHz	ICC	CA
Shah et al.(28)	2009	USA	40 (n.a.)	n.a.	3	>20 ONSD scans	LC	SR	Same session	Axial Coronal	10-5 MHz (brand n.a.) 13-5 MHz (brand n.a.) 8-5 MHz (brand n.a.)	n.a.	CA

Shrestha et al.(26)	2018	India	27 (29.6%)	27.4	4	1 obs. > 200 ONSD scans 3 obs. 10 scans	LC	SR	Same session	Longitudinal	Micromaxx 6-13 MHz	n.a.	CA

CA = Cronbach's Alpha
E_O = Experience observers
ICC = Intraclass Correlation Coefficient
LC = Labatory conditions

LoA = Limits of agreement
MRM = Method of repeating measurements
n.a. = Not available
n.c. = Not clear

NO = Number of observers
NP = Number of study
ORA = Offline reassessment

Rx = Reliability coefficient
SR = Scan-rescan
TBM = time between consecutive measurements

Table 1. Study characteristics

Techniques

Several techniques were used to measure the ONSD, as depicted in Figure 2. Asghar et al.[21], Bäuerle et al.[22,23], Lochner et al.[24], Maissan et al.[25] and Shrestha et al.[26] used the longitudinal technique. The probe is placed temporally on the upper eyelid to measure the ONSD. Mean ONSD's ranged from 3.40 to 6.02 mm. Three studies[27,] used axial measurements where the probe was placed horizontally on the medial upper eyelid. Sound waves pass through the cornea and lens.

Figure 2. Probe placement of different measurement techniques. A shows longitudinal measurements, with the probe placed temporally. B shows axial measurements. The probe is placed medially on the upper eyelid in horizontal position Sound waves pass through the cornea and lens. C Turning the probe 90 degrees to a vertical position results in axial measurements in sagittal plane. D depicts coronal measurements by placing the probe infraorbitally. The probe is placed on the lower eyelid. E represents coronal measurements by placing the probe laterally.

Mean ONSD of axial measurements had a range of 3.39 - 4.73 mm. Ozturk et al.[27] also utilized a different axial technique, turning the probe vertically. ONSD was measured axially, in a sagittal plane. ONSD means of 4.24 – 5.34 mm were found. Coronal measurements of the ONSD were performed by Shah et al.[28] and Amini et al.[29] Shah et al.[28] placed an intracavitary probe laterally on the eyelid, while Amini et al.[29] placed the probe infraorbitally. ONSD means ranged from 2.81 to 4.55 mm.

Measurements were repeated in most studies. Only Bäuerle et al.[23] determined intra-observer variability by reassessing previously recorded images of ONSD measurements. Measurements were repeated in the same session in seven out of nine studies. Bäuerle et al.[23] and Ozturk et al.[27] repeated ONSD measurements on another day. LoA, ICC and CA were used to quantify observer variability. For more details, see Table 1.

Quality Assessment

Generally, studies scored well on reporting measurement process. Studies scored less on reporting observer characteristics and statistics. All studies reported precisely what device was used to measure the ONSD. Measurement technique was described in detail as well. Six out of nine studies did not clearly define the ONSD. Measurements between observers were conducted independently in all studies, i.e. observers were unaware of the results of other observer's measurements. Bäuerle et al.[23] and Ozturk et al.[27] performed measurements *per observer* independently, as there was an interval of several days between the measurements. Measurements *per observer* by Maissan et al.[25] were performed independently, as observers were unaware during consecutive measurements, when an intervention took place that could affect the ICP. Non-independent measurements may influence outcomes of consecutive measurements.

Studies that reported ICC, did not specify which ICC was used. Confidence intervals were lacking for reliability coefficients in five studies. Two studies [22] used CA to quantify intra-observer variability. This parameter is not suited for intra-observer variability.[30] None of the studies discussed the clinical consequences of their results on observer variability explicitly. Further details on quality assessment are provided in Online Appendix B.

Intra-observer variability

The SEM_{intra} is calculated for six studies. It was not possible to calculate SEM_{intra} for Ozturk et al.[27], Shah et al.[28] and Shrestha et al.[26] The SEM_{intra} of the study of Maissan et al.[25] is based on ONSD measurements, without intervention that could alter ICP. Other studies did not feature interventions at all. Amini et al.[29] featured two observers; one observer performed axial measurements and the second observer took coronal measurements. Other studies only featured longitudinal measurements. SEM_{intra} of the longitudinal measurements of the left and right eye had a range of 0.104 – 0.413 mm. Corresponding MDD ranged from 0.288 to 1.114 mm (6.74% - 24.87% of corresponding mean ONSD) Further details are provided in Table 2.

Study	Observer	SD_L	SD_R	R_L	R_R	SD_d	SEM_L	SEM_R	MDD_L (%ONSD)	MDD_R (%ONSD)
	Longitudinal measurements									
Asghar et al.(21)	1	0.31	0.35	0.86	0.88	-	0.131	0.121	0.363 (7.40%)	0.336 (6.9%)
Bäuerle et al.(22)	1	0.6	0.6	0.97	0.95	-	0.104	0.134	0.288 (5.33%)	0.371 (6.74%)
	2	0.7	0.6	0.93	0.92	-	0.185	0.170	0.513 (9.50%)	0.471 (8.72%)
Bäuerle et al.(23)	1	-	0.49	-	-	0.22	-	0.156	-	0.412 (7.59%)
Lochner et al.(24)	1	0.68	0.63	0.69	0.69	-	0.379	0.350	1.050 (17.56%)	0.972 (16.15%)
	2	0.78	0.64	0.72	0.72	-	0.413	0.339	1.144 (19.46%)	0.939 (15.8%)
Maissan et al.(25)	1	0.6	-	-	-	0.5	0.354	-	0.980 (19.21%)	-
	2	-	0.6	-	-	0.5	-	0.354	-	0.980 (18.49%)
	Axial measurements									
Amini et al.(29)	1	0.62	0.73	0.71	0.72	-	0.333	0.368	0.925 (20.64%)	1.071 (22.64%)
	Coronal measurements									
Amini et al.(29)	2	0.84	0.79	0.76	0.79	-	0.412	0.362	1.114 (24.87%)	1.003 (22.04%)

Measurements are presented in millimeters.
MDD_{L-R} = Minimal detectable difference of the left and right eye
R_{L-R} = Reliability coefficient of the left and right eye
SD_d = Standard deviation of the difference
SD_{L-R} = Standard deviation of the left eye and right eye
SEM_{L-R} = Standard error of measurement of the left and right eye

Tabel 2. Intra-observer variability. Standard error of measurement and minimal detectable differences of all measurement techniques.

Study	N_O	SD_{pL}	SD_{pR}	R_L	R_R	SD_D	SD_{dL}
	Longitudinal measurements						
Bäuerle et al.(22)	2	-	-	-	-	-	0.37
Bäuerle et al. (23)	2	-	-	-	-	-	-
Lochner et al.(24)	2	-	-	-	-	-	0.37
Maissan et al.(25)	2	-	-	-	-	0.6	-
Shrestha et al.(26)	2	0.390 (O_{1-2})	0.530 (O_{1-2})	0.72	0.82	-	-
	2	0.334 (O_{1-3})	0.443 (O_{1-3})	0.81	0.71	-	-
	2	0.347 (O_{1-4})	0.473 (O_{1-4})	0.80	0.81	-	-
	3	0.334 ($O_{2,3,4}$)	0.444 ($O_{2,3,4}$)	0.80	0.88	-	-
	Axial measurements						
Ozturk et al.(27)	4	-	0.569	-	0.679	-	-
	4	-	0.563	-	0.683	-	-
Shah et al .(28)	3	-	0.394 (10-5 MHz)	-	0.58	-	-
	3	-	0.412 (13-6 MHz)	-	0.41	-	-
	3	-	0.432 (13-6 MHz)	-	0.39	-	-
	Axial measurements, sagittal plane						
Ozturk et al. (27)	4	-	0.544	-	0.700	-	-
	4	-	0.561	-	0.718	-	-
	Coronal measurements						
Shah et al .(28)	3	-	0.244	-	0.590	-	-

Measurements are presented in millimeters.
N_O = number of observers
SD_{pL-R} = Pooled standard deviation of the left eye and right eye

Table 3. Inter-observer variability. Standard error of measurement and minimal detectable differences of all measurement techniques

SD_{dR}	SEM	MDD (%ONSD)	SEM_L	SEM_R	MDD_L (%ONSD)	MDD_R (%ONSD)
0.38	-	-	0.262	0.269	0.725 (13.43%)	0.745 (13.67%)
0.51	-	-	-	0.361	-	0.996 (18.34%)
0.3	-	-	0.282	0.212	0.725 (12.23%)	0.588 (9.83%)
	0.424	1.176 (22.61%)	-	-	-	-
-	-	-	0.206	0.225	0.571 (16.57%)	0.624 (18.06%)
-	-	-	0.146	0.239	0.405 (11.59%)	0.662 (19.16%)
-	-	-	0.155	0.210	0.430 (12.25%)	0.582 (16.49%)
-	-	-	0.149	0.154	0.413 (11.88%)	0.427 (12.31%)
-	-	-	-	0.322	-	0.896 (18.10%)
-	-	-	-	0.317	-	0.879 (17.76%)
-	-	-	-	0.255	-	0.707 (18.04%)
-	-	-	-	0.316	-	0.876 (23.61%)
-	-	-	-	0.337	-	0.934 (24.45%)
-	-	-	-	0.298	-	0.827 (16.95%)
-	-	-	-	0.298	-	0.827 (16.84%)
-	-	-	-	0.186	-	0.432 (14.85%)

R_{L-R} = Reliability coefficient of the left and right eye
SD_d = Standard deviation of the difference
SEM_{L-R} = Standard error of measurement of the left and right eye
MDD_{L-R} = Minimal detectable difference of the left and right eye

Inter-observer variability

It was possible to calculate the SEM_{inter} for seven studies. The study of Asghar et al.[21] featured only one observer. In the study of Amini et al.[29], each observer used a different technique to measure the ONSD. Shah et al.[28] used three different probes to measure the ONSD; the 10-5 MHz and 13-6 probe were utilized to measure axially. The 8-6 MHz probe was used for coronal measurements. Shrestha et al.[26] compared multiple combinations of observers. No overall SEM could be calculated. Ozturk et al.[27] provided data on observer variability of measurements for two axes; axial and axial in a sagittal plane. Each observer performed these measurements on two separate occasions. SEM_{inter} for longitudinal measurements ranged from 0.146 to 0.425 mm. Corresponding MDD ranged from 0.405 mm to 1.176 mm (9.83% - 19.16% of corresponding mean ONSD) Further details are presented in Table 3.

Discussion

This is the first systematic review to give an overview of the inter- and intraobserver variability that has calculated the SEM and MDD of ultrasonographic measurements of the ONSD in healthy adults. The largest SEM_{intra} of longitudinal measurements was 0.413 millimeters. This means that we can be 95% confident that the “true” value of an index measurement of 5 millimeters would be in between 4.2 and 5.8 millimeters.[14] The corresponding MDD is 1.1 mm, which implies one can be 95% certain a difference of 1.1 mm in ONSD can be attributed to actual change in ICP.

Our results conflict with the results of Ballantyne et al.[31], one of the most cited articles regarding observer variability of ultrasonographic measurements of the ONSD. Ballantyne et al.[31] found significantly smaller values, both for intra- and inter observer variability. We could not include this article, as it was not possible to calculate SEM for this study. The relatively large MDD’s found in this review urge caution when interpreting index measurements and consecutive measurements of the ONSD. One must realize measurements in the included studies were performed under ideal, controlled conditions. It’s quite possible the SEM and MDD are higher in stressful situations, e.g. during primary survey in the ER after traumatic brain injury or in prehospital setting. Of note, SEM differed notably across studies. SEM_{intra} and SEM_{inter} of longitudinal measurements had a range of 0.108 - 0.413 mm and 0.262 - 0.424 mm respectively. This translates to MDDs ranging from 0.299 to 1.1144 mm and 0.762 to 1.1176 mm, substantial differences on the scale of ONSD measurements.

A variety of statistical techniques was used to quantify observer variability. Due to this heterogeneity, we were not confident to synthesize generic SEM’s per measurement technique. Providing auxiliary material online as suggested by Kottner et al.[19] e.g. more details on results, or even raw data, would allow for quantitative meta-analyses and more precise estimations of measurement error.

Mean ONSD in this review ranged from 2.8 to 6.02 mm. Schroeder et al.[7] found mean ONSD values of 4.78 mm (95% CI 4.63 – 4.94), measured by ultrasound. Still, studies included in Schroeders ‘ meta-analysis showed a broad range of mean ONSD and confidence intervals, suggesting there is considerable individual variety in ONSD values. This complicates the interpretation of an ONSD index measurement of an individual patient regarding the status of the ICP. Different measurement techniques may also have contributed to the range of ONSD in our review.

Our quality assessment using the guidelines proposed by Kottner et al.[19] revealed several strong points among the included studies in reporting reliability or agreement. Authors reported the measurement device, technique and measurement process meticulously. However, this systematic review also revealed there is room for methodological improvements to more accurately assess observer variability of this technique.

Firstly, the margins of the ONSD were not clearly defined in six out of nine studies. This complicates interpreting results, as it is not clear what is measured exactly. Uncertainty about the margins of the ONSD among observers may have contributed to observer variability. The optic nerve sheath is filled with cerebrospinal fluid, which appears as a bilateral hyperechoic line around the hypoechoic optic nerve. The ONSD is the distance between the external boundaries of this line.[32,33] These margins may not always be clearly visible, e.g. in suboptimal measurement conditions. Artifacts have also been mentioned as possible hindrance.[34]

Secondly, none of the studies that used an ICC as a reliability coefficient defined it. Multiple ICC exist, each with its specific function.[35] Choice of ICC depends on the goal and design of the study.[30] Some authors used CA, i.e. $ICC_{consistency}$. $ICC_{consistency}$ leaves room for systematic errors. An example: If observer 1 consistently rates the ONSD 1 mm smaller than observer 2, it results in an $ICC_{consistency}$ of 1, the highest score. This is rather unpractical in clinical context. When measuring the ONSD, absolute agreement between observers is most relevant. Absolute agreement can be assessed with $ICC_{agreement}$.[35] This parameter may have been more appropriate compared to $ICC_{consistency.}$

Thirdly, confidence intervals of reliability coefficients were not reported in five studies. Confidence intervals offer valuable information for the interpretation of results.[36] The lower limits are particularly important, when one has to judge whether a measurement device comes with an adequate level of reliability or agreement.

Fourthly, the included studies featured only a limited number of observers (1-4) with a median of two observers that performed measurements in laboratory conditions. Having 10-20 observers rate a subject on several occasions in circumstances that reflect daily practice allows for more realistic estimation of clinical observer variability.[37]

Following, in agreement or reliability studies observers' training for, or experience with a measurement method has to be reported precisely. It is one of the cornerstones that eventually lead to the level of reliability or agreement between observers. Without this information, clinicians are hindered to learn to perform measurements identically and obtain similar results.

Lastly, none of the authors discussed the clinical relevance of the reported outcomes. Reliability scores were scored as "excellent," or "good." Qualitative grading does not provide sufficient information to judge whether a measurement device is suited for its purpose. Here we need to have insight in the real life anatomical variance as well, preferably measured with the gold standard. Limits have to be set in this respect. Which amount of error is allowed in clinical decision-making? Does the studied measurement device meet said limits? The answer on these questions will differ per measurement device and its aim.

Limitations

There are limitations to this review. First of all, none of the included studies had access to direct ICP measurements. ICP physiologically fluctuates over time, albeit slightly.[38] Coughing and sneezing also affect ICP.[39] Variation over time may have contributed to measurement error.

Secondly, the SEM was calculated indirectly, as opposed to direct calculation. This poses drawbacks: ICC was not defined in any of the papers. Different ICC's result in a different SEM. Besides, indirect calculation does not always take into account systematic error.[15] Imprecisions can be avoided by calculating the SEM directly. Through analysis of variance SEM can be calculated precisely.[14,40] This allows for further analysis, including 95% confidence intervals as suggested by Bland[41] and statistical comparison of SEM, e.g. SEM of different measurement techniques.

Thirdly, methodological aspects of the included studies could have influenced the reported observer variability in the included studies. All of the above limitations may have contributed to the found range of SEM and MDD across studies.

Lastly, it is possible we missed relevant articles. We tried to limit this by conduction a systematic search in multiple databases on several occasions.

Recommendations

Measures like SEM, MDD, and LoA translate measurement error to parameters that are useable in clinical practice. It's often unclear what the clinical implications are of an ICC of, say 0.8. One does not know how it affects consecutive measurements. In contrast, a MDD provides a distinct cutoff value that is easy to use in clinical settings. We encourage the use of these parameters in future studies regarding agreement between observers.

SEM and MDD of measurements in a population at risk for increased ICP are required for this method to be used as a screening tool or monitoring of ICP. Assessment of the

ONSD should be linked to direct ICP measurements to calculate observer variability of ONSD measurements in a population that would benefit most of it. Designing such studies methodologically correctly is challenging, but not impossible.

Automated algorithms for ONSD measurements could be used in the future. A promising attempt has been published recently.[42] Using automated algorithms to interpret ultrasound images may reduce observer variability due to human error.

Finally, as advocated by van Genderen et al.[37], internationally accepted standards are necessary on reliability studies, similar to the CONSORT Statement for Randomized Controlled Trials. Universal guidelines allow for a more systematic approach to designing and reporting this type of studies. This in turn leads to studies that are reproducible and more easily incorporated in clinical practice.

Conclusion

Great progress has been made on ultrasonographic measurements of the ONSD over the last two decades. As a noninvasive way for ICP measurement it could be of substantial value in the (pre)hospital setting. Yet, there are obstacles to overcome. This systematic review has revealed measurement error may be considerably larger than previously thought. Studies, emphasizing on accurate methodology and statistics, are needed to determine observer variability of different ONSD measurement techniques, before the transition of ONSD measurement is to be made from research setting to clinical practice.

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CHAPTER 11

General discussion

This thesis focuses on some of the challenges that prehospital care providers have to deal with in patients suffering from severe traumatic brain injury (sTBI) and possible adjustments in routine strategies that may improve outcome.

Monitoring and treatment of sTBI

Nowadays sTBI patients in the intensive care unit are treated more and more with targeted management for specific patients categories based on age, sex and disease mechanisms. Invasive monitoring of intracranial pressure (ICP), cerebral blood pressure (CPP), local neuronal oxygen pressure and extraction fractions and brain damage specific enzyme concentration in the blood can help to tailor treatment regimes in specific patients.[1]

In prehospital settings these invasive methods are not available. Treatment is based on in fact a "black box approach" initiated if sTBI with raised ICP is suspected based on the mechanism of injury and the clinical signs (GCS<9, Cushing triad).[2] Most evidence that supports this approach is based on young male TBI patients but the incidence of elderly patients that suffer from sTBI is increasing.[3] Some kind of monitoring of the pressure in the head would be of great help to adjust treatment strategies in prehospital settings. Inserting intracranial pressure probes on-scene is not an option but a less invasive tool would be of great help to prehospital care workers. In **chapter 2** we evaluated a non-invasive indirect tool to measure pressure changes in the head. We demonstrated that ultrasonographic measurement of the optical nerve sheath diameter (ONSD) behind the eyes is highly correlated with direct ICP changes measured with an intracranial pressure probe. The changes in ICP before, during and after suctioning of the endotracheal tube resulted in simultaneous changes in ONSD in ICU patients. In all cases ONSD reverted to baseline levels simultaneous with a decrease of ICP, directly after tracheal manipulation had stopped. So, changes in ICP are accurately reflected by changes in ONSD at the same day or several days after trauma. At low levels ICP (8-10 mmHg) changes do not affect the ONSD. When ICP rises, a linear correlation is seen between ONSD and ICP. In the included patients ONSD ≥ 5,0 mm is the optimal cut-off value for detecting elevated ICP (> 20 mmHg). However the best cut-off point of ONSD representing a raised ICP is still under debate and is suggested to be related to sex, age and ethnicity of the patient. Besides that the elasticity of the sheath seems to differ between individuals due to differences in connective tissue build up and distribution in the sheath. Prior shear stress on the sheath during extreme rises in ICP may alter the elasticity due to plastic deformation and change the ONSD response to ICP changes. In **chapter 3** we did a re-examination of our data from the previous study described in **chapter 2** and the data presented by Knut Helmke and Hans-Christian Hansen, the founding fathers of ONSD measurements. We found that ex vivo optical nerve sheath plastic deformations occur at levels of pressure commonly seen in patients with raised ICP. This may illustrate why a meta-analysis failed to identify a single cut-off point in ONSD in presence of raised ICP. Using ONSD measurements to determine the presence or absence of increased ICP, based on a single cut-off point, could be unreliable if former episodes of raised ICP have occurred. For this reason measurement of the ONSD is considered a qualitative rather than quantitative assessment of ICP that can be used to evaluate effects of certain interventions on the intra cranial pressure. Ideally a benchmark measurement of the ONSD is taken in every subject included in a study before any ICP changing intervention is done so follow-up ONSD measurements can be interpreted.

Treatment in prehospital setting

The Brain Trauma Foundation calls for a secured airway in their prehospital guidelines by "the most appropriate means" available for unconscious patients (GCS <9) and/or low peripheral oxygen saturation measurements (<90%) under maximal oxygen therapy. (NRM 15l. O_2)[3] Nevertheless literature is inconclusive about the benefits or harm of prehospital endotracheal intubation (ETI).[1,4] Overall population based studies rather than targeted studies defining patients groups or adjusted treatment strategies are likely to fail to prove benefit of any neuroprotective interventions.[5] The inconsistent findings reported on prehospital airway management may be caused by this mechanism. In large studies on heterogenic patients groups no outcome benefit was found in pooled data on prehospital ETI by various prehospital care workers performing drug assisted and non-drug-assisted intubations.[1,4]

In **chapter 2** we have seen ICP and ONSD responses to tracheal suctioning even in the severest injured TBI patients (GCS = 3). This suggests that intubation increases ICP in sTBI patients especially if intubated without any anesthetic medication. This effect of laryngeal stimulation on ICP may be due to sympathetic stimulation in the airway. In ENT surgery intravenous lidocaine is used to alter this effect at the end of the surgical procedure to prevent from coughing and gaging during waking up from anesthesia.

In **chapter 4** we evaluated the effect of ETI on ICP by measuring ONSDs before, during and after endotracheal intubation under standardized general anesthesia for routine surgical procedures in the operating room of our hospital. ONSDs distended in all patients during ETI and ETI attempts. After ETI was successfully performed ONSDs did not return to baseline levels due to the presence of the endotracheal tube between the vocal chords. Participating patients were randomized in two groups. In the intervention group 1,5 mg/kg intravenous lidocaine was added to their induction medication. The control group received a same amount of NaCl 0,9%. Which medications was administered was blinded to the researchers. ONSD distended less in the lidocaine group and returned to baseline levels after 10 minutes of continuous tube position between the vocal chords in the lidocaine group. These findings suggest that adding lidocaine to the medication for general anesthesia attenuates the ICP rising effect during and after ETI. Nevertheless a gentle intubation in as little as possible attempts may prevent from repetitive spikes in ICP during ETI that may alter perfusion of the injured brain.

When looking in more detail to the experience and exposure of the airway provider, poor experience comes with increased mortality in TBI patients.[6] In **chapter 5** we evaluated the first pass and overall success rates of ETI by different experienced prehospital workers using direct or video laryngoscopy for ETI in the prehospital setting. The use of videolaryngoscopy was associated with an increase of the first pass success rates of ETI by ambulance nurses from 45.5% with direct laryngoscopy to 64.8% and the overall success rates from 58.4% and 77.2% respectively. Despite these results the success rates with both direct and video laryngoscopy by ambulance nurses with the current training program are too low to continue the practice of ETI in prehospital settings. ETI by ambulance nurses in trauma patients was associated with a high incidence of unrecognized esophageal tube position on HEMS arrival despite the use of videolaryngoscopy. Therefor airway training programs should be intensified for ambulance nurses in the Netherlands or prehospital intubations should only be performed by HEMS doctors with extensive experience and exposure. **Chapter 6** describes a systematic review of the literature on the learning curve for endotracheal intubation using direct laryngoscopy. We found that in mostly elective circumstances at least 50 ETIs with no more than two intubation attempts need to be performed to reach a success rate of at least 90% in novel airway providers. Leaving alone that the incidence of difficult airways in non-elective settings is up to 20 times higher. Taking this factor into account, training for prehospital professionals should include a variety of exposures and should probably exceed 50 ETIs to successfully serve the most vulnerable patients. Videolaryngoscopy may shorten the learning curve of endotracheal intubation. The combination of intensified initial airway training programs and videolaryngoscopy may increase success rates but the low exposure to advanced airway management (3-6 intubations per ambulance nurse per year) may lead to skill atrophy and decrease success rates over time. For now the success rates with both direct and video laryngoscopy by ambulance nurses with the current training programme are too low to continue the practise of ETI by ambulance nurses.

Immobilization issues in sTBI patients

After the patient is intubated by the most experienced airway provider at the scene and proper neuro-anesthesia is started, immobilization to prevent from further neurologic deterioration is indicated. Traditionally all trauma patients are immobilized using a rigid cervical collar that prevent from cervical movement in combination with a spine board or a vacuumed matrass during transportation. Previous literature had stated some concerns about the jugular compression by a rigid cervical collar that may impair venous drainage from the injured head and increase ICP.[7] Venous drainage is one of the mechanisms described by Kelly and Monroe that can compensate for ICP increase after trauma.[8] In **chapter 7** we describe that application of a rigid cervical collar in healthy volunteers results in a statistically significant increase of the ONSD. This suggests that ICP will rise when a rigid cervical collar is applied. In healthy volunteers, this is probably clinically irrelevant due to maintained cerebral blood flow (CBF) by autoregulation mechanisms but may cause harm in TBI patients suffering from raised ICP. In patients with swelling and bleeding of the brain after trauma, the jugular compression by the rigid collar may impair the pressure compensation mechanism and worsen secondary brain injury. Cervical collars are no longer routinely used in the Dutch prehospital care. Only in mechanically entrapped patients in vertical sitting position, for example behind the steering wheel of a crashed car, a rigid cervical collar can be applied to release the weight pressure of the head on the injured spine.

Transportation issues of sTBI patients

After stabilization and immobilization patients should be transported directly to a Level 1 trauma center for better outcome.[8] Helicopter transportation introduces concerns about the nose down flying pattern of the helicopter leading to a Trendelenburg position of the patient. Gravitational force will force venous blood into the head leading to ICP increase. Dutch Lifeliners are Airbus EC-135 type helicopters. Due to the design of the aircraft patients are positioned in head in flight direction. When a helicopter is in hover flight the lift of the rotordisc is equal to the weight of the helicopter. To gain speed the rotordisc needs to be tilted forward. The horizontal component of this lift vector will increase the airspeed in the "nose down" flying pattern. In the EC-135 the fuselage attitude changes in the same direction. At least during lift off and landing the head rest of the gurney had to be in supine position due to aviation regulations and the user manual of the gurney used in the EC-135 helicopters. In **chapter 8** we describe our experiment that shows that ONSD increases during flying in volunteers on the gurney in supine and thereby an in-flight Trendelenburg position. This suggests that helicopter transportation may impair brain perfusion during the flight in patients suffering from sTBI. Our experiment shows that raising the headrest before lift-off will compensate for this effect on ONSD. After publication of these data in 2018 Dutch helicopters are equipped with new gurneys that are certified for lift off and landing in head up position.

Nevertheless most patients (87,2%) are transported by road ambulances because the mean distance to a level 1 trauma center is 30 km by road in most areas in the Netherlands.[2] Ambulance drivers are trained to drive as smoothly as possible but emergency braking's do occur during road transportation. In **chapter 9** we describe our study that investigated the relationship between the fluid shifts during ambulance braking and ONSD distention in 20 volunteers. The results demonstrate that the deceleration force of braking increases the ONSD and hence rises ICP during ambulance transportation in supine position. We did the same experiment with the headrest in 30 degrees upright position with the same volunteers. In 15 volunteers there was no effect on ONSD during braking. In the other 5 volunteers the ONSD distention during braking was far less than in supine position. Based on these findings we suggest to raise the headrest as soon as possible in prehospital care if systemic blood pressure is in normal or supra-physiological range. Hopefully these measures will help to reduce secondary brain injury in sTBI patients.

Sample size and population issues

Ultrasonographic measurement of the ONSD as a noninvasive technique has helped us to investigate the effect of some “routine procedures” in prehospital care for sTBI patients. We think we have made some improvements in these “routine procedures” in favor of patient outcome when it comes to airway management, immobilization and transportation strategies.

Nevertheless, our data come from small experiments with volunteers or patients without intra cranial pressure issues. To investigate the effects of rigid cervical collars, helicopter or road ambulance transportation on ICP in sTBI patients, larger studies are needed in sTBI patients in these circumstances.

Most of our studies are proof of principle experiments because no valid data was available to calculate the correct sample size at the time the studies were designed. Data need to be confirmed in follow up studies that are statistically powered based on our results.

ONSD measurement issues

The sonographic technique is reported to be rather easy to learn and has been proven to have a low intra and inter observer variability by Ballantyne et al.[9] Nevertheless we experienced difficulties to reproduce data by different sonographers under the same circumstances as described in **chapter 7**. **In chapter 10** we evaluated the intra and interobserver variability of recent literature on ONSD measurements in a systematic review using a mathematical standard error of measurement (SEM) and minimal detectable difference (MDD) to evaluate intra and interobserver variability. Our results conflict with the results of Ballantyne et al., one of the most cited articles regarding observer variability of ultrasonographic measurements of the ONSD. Ballantyne et al. found significantly smaller values, both for intra- and inter observer variability.[9] We could not include this article, as it was not possible to calculate a SEM for our review. The relatively large MDD’s found in our review urge caution when interpreting index measurements and consecutive measurements of the ONSD to evaluate ICP in clinical practise. One must realize measurements in the included studies were performed under ideal, controlled conditions. It’s quite possible that the SEM and MDD are higher in stressful situations, e.g. during primary survey in the ER after traumatic brain injury or in a/the prehospital setting. ONSD measurement can be used for research purposes if the sonographer is well trained and performs all measurements in the same subject.

Recommendations and future research suggestions

Technique of ONSD measurement

The margins of the ONSD have to be clearly defined and ideally been standardized internationally in future research. Uncertainty about the margins of the ONSD among observers may have contributed to observer variability in the past. The optic nerve sheath is in fact a dural sleeve filled with cerebrospinal fluid and the nerve itself, which appears as a bilateral hyperechoic line around the hypoechoic optic nerve. The ONSD is the distance between the external boundaries of this line.[10,11] When measuring the ONSD, absolute agreement about technical issues between observers is most relevant.

Some methodological improvements need to be made to become more accurate in assessing observer variability of the technique of ONSD measurements. The included studies in **chapter 10** featured only a limited number of observers (1-4) with a median of two observers that performed measurements under ideal standardized conditions. Having 10-20 observers rate a subject on several occasions in circumstances that reflecting daily practice allows a more realistic estimation of clinical observer variability.[12]

Applied artificial intelligence in the ultrasound machine itself that can measure and calculate the ONSD may diminish intra and inter observer variability issues in the future. These techniques are already used in other sonographic domains as "auto-biometrics" that can calculate fetal age from automatically measured femur length and skull circumferences for instance in obstetric evaluation of unborn children excluding SEM and sonographer interpretations and variations.

Our systematic review has revealed that measurement errors may be considerably larger than previously thought. Studies, emphasizing on accurate methodology and statistics, are needed to determine observer variability of different ONSD measurement techniques, before the transition of ONSD measurement is to be made from research setting to clinical practice.

Data management

To monitor patient outcomes in the Dutch prehospital field we urgently need a national data registration bank containing all (pre)hospital data from EMS, HEMS and hospitals. All services need to gather the same comparable patient data (standardized datasets) to facilitate future research. In my opinion we need centralized leadership from our government to unite all 24 EMS regions and 4 HEMS stations in one national prehospital emergency care organization as has been done with our police organizations a couple of years ago. In the current situation too many people in too many organizations with too many different cultures and interpretations are producing inconsistent and useless data prohibiting from proper national research and quality improvements.

We need more prospective randomized clinical trials in the Dutch (pre)hospital setting in order to evaluate and possibly improve our prehospital strategies for sTBI patients. Furthermore evaluation of the “black box” approach that Dutch HEMS use on patient outcome is required. Moreover, we need to evaluate the effect of our prehospital airway management strategies. Do our efforts lead to a better patient outcome or do we have to change our workflow?

I was recently asked to discuss our prehospital approaches in sTBI patient on a national congress of the Dutch society of neurosurgeons. Wat I have learned from the feedback and discussion afterwards is that Dutch trauma centers differ in their treatment regime of sTBI patients. As I was professionally born and raised in the Erasmus Medical Center I was used to the aggressive strategies we use in sTBI cases in our hospital. The trauma team for sTBI patients consists at least of an Anesthesiologist, a Trauma surgeon and a resident of Neurosurgery. The primary survey of the trauma protocol is reduced to the most essential vital signs and interventions when any signs of brainstem herniation are present. This means that if Airway, Breathing and Circulation are patent the patient will get a CT scan of the brain right away and will go directly to the operating room(OR) if an intracranial intervention is indicated. I like to call it our ABCT-OR protocol. Secondary survey has to be completed after the neurosurgical intervention. I was surprised that this ”Rotterdam approach” is quite unique in the Netherlands. The other trauma centers tend to complete the primary and secondary survey and send the patient to the ICU to wait for the OR if operated at all. These different strategies have to be evaluated to learn more about the impact on outcome of these regimes.

But in the end the best treatment of TBI in general is preventing it to happen. Most TBI in high income countries result from falls in the elderly and road traffic accidents in younger people. Most sTBI in the Netherlands are traffic related injuries (53.6%). About a fifth (21,8%) of all sTBI cases in the Netherlands result from road traffic accidents with cyclists. Although mandatory helmet use decreased injury severity by 63-88% in other western countries a helmet law isn’t implemented in the Netherlands yet.[13-15] Promoting helmet use in Dutch traffic can reduce sTBI due to accidents with cyclists and is by far the most effective measure society can take to reduce the incidence of annual sTBI cases.

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CHAPTER 12

Summery

Summary in Dutch
(Nederlandse samenvatting)

PhD-portfolio and list of publications

Dankwoord

Summary

Traumatic brain injury (TBI) is the leading cause of death in young people. Alarmingly, the incidence of TBI is increasing worldwide. The primary injury to the brain can lead to bleeding and swelling of brain tissue in severe cases. Because space is limited in the head, expanding hematoma's and swellings in the brain can increase the intracranial pressure (ICP). Especially in the early posttraumatic period, elevated intracranial pressure is associated with a high risk of secondary ischemic brain damage. ICP lowering treatments should be started as soon as possible in order to optimize cerebral perfusion pressure (CPP) and save brain tissue.

In the Netherlands a physicians staffed emergency medical service (P-HEMS) can assist the ambulance service in these high complex cases by restoring oxygenation, brain perfusion and lowering metabolic demands of the brain. After initial stabilization on-scene, the patient will be transportation to a level 1 trauma center as fast as possible for further treatment. Most of the Dutch P-HEMS strategies of prehospital anesthesia, advanced airway management, spinal immobilization, hypertonic fluids and type of transportation are based on expert opinion, traditions and common sense instead of (strong) scientific evidence.

In this theses we studied the effects of some of these standardized prehospital medical interventions on the intracranial pressure (ICP). To do so, we first evaluated the usability of a non-invasive bedside technique to measure changes in ICP. Because the optical nerve sheaths that surround the optical nerves are in continuum with the meninges that surround the brain, cerebrospinal fluid (CSF) can percolate freely in these sheaths when ICP changes. The ONSD behind the eye increases when more CSF percolates in the sheath. This diameter can be measured with ultrasonography through a closed eyelid. In **chapter 2** we compared sonographic measured optical nerve sheath diameters (ONSD) to direct invasive ICP registrations (gold standard) in TBI patients in the intensive care unit. ICP is known to temporarily elevate during certain nursing procedures and normalizes after the procedure is stopped. We found that ONSD distention during ICP rising interventions happens simultaneously but also returns to the baseline diameter with the normalizing ICP level. The correlation between ONSD and ICP was high ($R^2 = 0,80$) in the 18 TBI patients that we included. We concluded that ultra sonographic measurement of the ONSD is a simple and rapid measurement, for detecting elevated ICP as well as immediate changes in ICP. Therefore, it can be used as a tool to monitor the effects of our routine treatment strategies on ICP.

The fact that ONSD represents ICP is based on an assumption of a linear pressure–diameter relationship in the tissue. Although such a linear relationship has been described in multiple papers and may be correct for small ICP changes, the effects of extreme pressures on the biomechanical properties of the tissue should also be considered. Larger changes in

ICP may result in plastic deformation, or irreversible changes to the tissue and affect the ONSD response to ICP changes afterwards. In **chapter 3** we described a post hoc analysis of human cadaveric ex vivo measurements of ONSD and our own results described in **chapter 2**. We found that plastic deformation occurs with distending pressure of 45 mm Hg and more, that results in a different pressure-diameter relationship after longer exposure to such pressures. Because of the possible presence of plastic deformation after high ICP's a cut-off point in ONSD representing high ICP (>20mmHg) in TBI patients can't be calculated. Therefore, sonographic measured ONSD distention should be considered to be a qualitative rather than a quantitative measure for increased ICP in the field or in research settings with TBI patients.

In this thesis we used ultrasonographic ONSD measurements to evaluate the effect of routine strategies on ICP in groups of non-TBI patients and volunteers.

To optimize oxygenation and ventilation in trauma care endotracheal intubation (ETI) is performed to secure the airway in severe TBI. In the Dutch prehospital situation this procedure is ideally performed by an experienced physician and under adequate anesthetic medication to minimize the number of intubation attempts and the ICP rising effects of laryngoscopy. Most evidence on this ICP rising effect of laryngeal stimulation during ETI is indirect and limited to experiments with tracheal suctioning instead of ETI. In **chapter 4** we described a double blinded randomized controlled study including 60 non-TBI patients who got intubated for elective surgical procedures in the operating room. In the control group (N = 30) we found that ETI under adequate anesthesia does increase the ICP and that the tube position between the vocal chords under continuous general anesthesia does not return to baseline ICP levels after the laryngoscope was removed from the mouth. Adding I.V. lidocaine (1,5mg/kg) to the induction medication of the intervention group (N = 30) in this experiment three minutes before ETI, attenuated the effect of ETI on ONSD and resulted in return to pre-intubation baseline ICP/ONSD levels after 10 minutes of continuous tube position between the vocal chords. This attenuating effect of lidocaine on the ICP response to ETI may be beneficial in TBI patients.

In **chapter 5** we evaluated the intubation success rates of the three groups in Dutch prehospital setting that perform ETI with direct or video laryngoscopy. Video laryngoscopy seems to increase both first pass and overall success rates of ambulance nurses and helicopter emergency medical service (HEMS) nurses. Nevertheless HEMS physicians have the best first pass and overall success rates due to high experience and exposure and should perform ETI in TBI patients to minimise the ICP rising effect of multiple ETI attempts that could compromise brain perfusion. In **chapter 6** we aimed to determine the number of ETIs a health care provider in training needs to perform to achieve proficiency within two attempts. This review of the literature showed that in elective circumstances, at least 50 ETIs were needed to reach a success rate of 90%. However, the evidence is heterogeneous, and the incidence of difficult airways in non-elective settings is up to 20 times higher compared to elective settings. Taking these factors into account, training should include a variety of exposures and should probably exceed 50 ETIs to successfully serve the most vulnerable patients with a high first-pass success rate.

Especially after head injury a high index of suspicion is required for possible cervical injuries dictating strategies of no or as little as possible movement of the neck during ETI and transportation.

For decades trauma patients have been immobilized with spine boards, rigid cervical collars and vacuum matrasses. Immobilizing a fractured limb or spine seems reasonable but there are some concerns about cervical collars impairing venous drainage from the head. This may be the case in TBI patients with raised ICP in which venous drainage serves as a pressure compensating mechanism in the head. In **chapter 7** we tested the possible effects of a rigid cervical collar on the ONSD and thereby ICP. We found that application of a rigid cervical collar significantly increases the ONSD in healthy volunteers with intact cerebral autoregulation. This suggests that ICP in TBI patients may increase after application of a collar and alternative immobilization strategies with less or no jugular compression should be considered.

After P-HEMS started ICP lowering therapy and strategies on-scene and the patient is immobilized on the stretcher, transportation to a level 1 trauma center should be initiated in the fastest possible way. Dutch HEMS use Airbus EC-135 and H-135 helicopters in which a patient is positioned head first in the flight direction. To gain speed the rotor disc needs to be tilted forward. (helicopter nose down tail up) The horizontal component of this lift vector will increases the airspeed. This results in a Trendelenburg position of the stretcher during acceleration and flight. In **chapter 8** we describe the effects of this nose down helicopter flight pattern and Trendelenburg position on the ONSD of healthy volunteers in supine position on the stretcher. During this position the ONSD distended, representing an increased ICP. Raising the headrest of the stretcher before lift-off compensates for this effect and prevented from a rise in ICP during helicopter transportation.

Because the Netherlands is a dense populated well developed country transportation times to level 1 trauma centers are 30 minutes on average by road ambulance. This is why most patients are transported by road after initial stabilization on-scene. Road transportation on the other hand has other challenges in TBI patients. Acceleration and deceleration have the potential to create pressure changes in the head that may worsen outcome. In **chapter 9** we described that due to fluid shift to the head ONSD and thereby ICP increases during deceleration of a transporting vehicle in healthy volunteers in supine position. Raising the headrest of the stretcher to 30 degrees reduces the effect of breaking on ICP. If mean arterial pressure is high enough (80-100mmHg) we recommend to raise the headrest 30 degrees during transportation in a helicopter or in an ambulance.

All studies in this thesis using songraphic ONSD measurements were performed with the same standardized technique: B-mode ultrasonography and ONSD measurements in the axial plane 3 millimeters behind the retina with a low mechanical index setting (MI = 0,2).

Every measurement comes with measurement error, stemming from the apparatus, the measurement technique, the observer, the context and circumstances under what the measurement was executed or combinations of these determinants. In **chapter 10** we reviewed the literature on the intra and inter observer variability of ONSD measurements. The standard errors of measurement and minimal detectable differences of ultrasonographic measured ONSD's in research settings with healthy participants urge caution in interpreting results acquired with this measurement method in clinical settings.

Samenvatting

Traumatisch hersenletsel wordt gedefinieerd als een veranderd functioneren van de hersenen nadat een kracht van buitenaf op het hoofd en de hersenen heeft ingewerkt tijdens een ongeluk. Anders gezegd: de schade die door een ongeval aan de hersenen ontstaat.

De klachten nadien kunnen variëren van milde tot matige klachten van aanhoudende hoofdpijn en concentratiestoornissen tot ernstige blijvende schade met persoonlijkheidsveranderingen, invaliditeit of de dood tot gevolg. Ernstig traumatisch hersenletsel is doodsoorzaak nummer één onder jonge, vooral mannelijke, ongevalsslachtoffers in de westerse wereld.

Naar schatting lopen per jaar wereldwijd 50 miljoen mensen hersenletsel op door een ongeval. Men gaat er vanuit dat ongeveer de helft van de wereldbevolking gedurende het leven in meer of mindere mate traumatisch hersenletsel oploopt. De kosten worden wereldwijd geschat op 350 miljard euro per jaar.

Door de toename van gemotoriseerd vervoer in ontwikkelingslanden en doordat ouderen langer fit en mobiel blijven in vooral de westerse wereld, neemt de incidentie van hersenletsel wereldwijd geleidelijk toe. Dit wordt ook wel 'de onopgemerkte epidemie' (the silent epidemic) genoemd.

Hoe vaak dit soort letsels precies voorkomen in een bepaalde stad of land is lastig vast te stellen omdat de incidentie in de verschillende regio's in de wereld op verschillende manieren wordt bijgehouden. Men schat dat er in Europa jaarlijks 300 mensen per 100.000 inwoners worden opgenomen in een ziekenhuis met hersenletsel na een ongeval. 12 mensen per 100.000 inwoners per jaar komen te overlijden als gevolg van dat hersenletsel.

In Nederland zijn dit jaarlijks 213,6 mensen per 100.000 inwoners die mild, matig of ernstig hersenletsel oplopen door een ongeval. 2,7 op de 100.000 mensen in Nederland lopen jaarlijks ernstig hersenletsel op. De meeste van deze mensen zijn man (70,9%) met een gemiddelde leeftijd van 46 jaar, maar variërend van 1 tot 97 jaar. 58,4% van deze ongevallen deden zich voor in het verkeer. 35,4% van de ernstige variant ontstond door een val van zekere hoogte. Minder dan 2 % ontstond door mishandeling en geweld. Van de verkeersslachtoffers waren 37,4% fietser. Dat is 21,4% van alle mensen die jaarlijks een ernstig hersenletsel oploopt. Ondanks dat is bewezen dat het dragen van een helm op de fiets de kans op ernstig hersenletsel kan verlagen, wordt in Nederland lang niet door iedereen een helm gedragen in het verkeer. Hier ligt de grootste kans voor de Nederlandse samenleving om met preventieve maatregelen ernstig schedelhersenletsel te voorkomen.

De dempende eigenschap van een helm kan de energie absorberen die anders op het hoofd zou inwerken. De zachte kwetsbare hersenen drijven min of meer los in de schedel. Deze schedel beschermt de hersenen in normale omstandigheden zoals bij hoofdstoten of het koppen van een bal tijdens een potje voetbal. Bij grotere impact beschermt de schedel de hersenen ook, maar kan daarna soms averechts gaan werken. Als tijdens een ongeluk het hoofd bijvoorbeeld hard tegen de grond smakt, worden de hersenen heen en weer geschud in de harde schedel. Op de plaatsen waar de hersenen tegen de binnenkant van de schedel zijn gebotst ontstaat letsel aan het hersenweefsel. Dit wordt *primair hersenletse*l genoemd. Bij zo'n primair hersenletsel kunnen bloedingen en zwellingen ontstaan in of bij de hersenen, waardoor er extra ruimte wordt ingenomen in het hoofd. De massawerking die ontstaat bij uitbreiding van de zwelling en bloeding kan ervoor zorgen dat de druk in de schedel toeneemt. Hoe hoger de druk in het hoofd, hoe hoger de bloeddruk moet zijn om nog bloed de hersenen in gepompt te krijgen.

Bijkomend nadeel is dat de hersenen, anders dan andere cellen in het lichaam, geen glucosereserves in de cellen kunnen opslaan als brandstof. Bovendien kunnen ze zonder zuurstof geen glucose verbranden tot energie. Dit betekent dat de hersenen continu afhankelijk zijn van de aanvoer van zuurstofrijk bloed met daarin voldoende glucose. Als de doorbloeding van de hersenen onmogelijk wordt door een verhoogde druk in het hoofd, zal vrijwel direct bewusteloosheid ontstaan en zullen de hersencellen beginnen met afsterven. Hoe langer de periode van hoge hersendruk duurt, hoe meer schade er ontstaat aan de hersenen. Deze 'verdrukkingsschade' wordt *secundair hersenletsel* genoemd die kan optreden na een ongeval. De primaire hersenschade is alleen te voorkomen of beperken met preventieve maatregelen zoals een fietshelm of zoals valbescherming tijdens werk op hoogte. Prehospitaal kan de secundaire hersenschade waarschijnlijk beperkt worden door zo snel mogelijk druk verlagende therapie te starten middels medicatie. Daarnaast kan door intubatie en beademing continu zuurstof worden aangeboden. Door te starten met bloeddrukondersteunende medicatie kan de bloeddruk op peil worden gebracht in de hoop dat daarmee weer doorbloeding ontstaat in de verdrukte delen van de hersenen.

Ondanks dat deze strategieën in veel leerboeken en behandelprotocollen zijn opgenomen is hier maar beperkt wetenschappelijk bewijs voor. Men vermoedt ook dat sommige technieken zelfs een averechts effect zouden kunnen hebben indien ze op een verkeerde manier of door een onvoldoende getrainde hulpverlener worden uitgevoerd.

In **hoofdstuk twee** van dit proefschrift vergelijken we een niet invasieve manier om de hersendruk te meten met de standaard manier die op de intensive care wordt gebruikt. In dit onderzoek hebben we geconstateerd dat het middels echografie meten van de diameter van de schede die om de oogzenuw (nervus opticus) loopt achter de oogbol een snelle en relatief makkelijke manier is om een indruk te krijgen van de drukveranderingen in het hoofd bij patiënten met traumatisch hersenletsel.

Met dit meetinstrument is het mogelijk om de interventies die worden gedaan in de (pre)hospitale zorg voor trauma patiënten met hersenletsel te evalueren bij mensen die geen druksensor in het hoofd hebben.

De schede rond de oogzenuw is een uitloper van de vliezen die aan de buitenkant om de hersenen liggen. De vloeistof waar de hersenen als het ware in drijven kan onbeperkt in de schede stromen als de druk in het hoofd hoger wordt. Meer vocht in de schede leidt tot een uitzetting van de diameter van de schede achter het oog, die met een echoapparaat in beeld is te brengen. Deze techniek dateert van het einde van de jaren negentig. Twee patholoog-anatomen uit Duitsland hebben in een studie bij overledenen, die hun lichaam ter beschikking hebben gesteld aan de wetenschap, de relatie onderzocht tussen de met echo gemeten diameter van de schede rond de oogzenuw en de druk in het hoofd. Zij hebben geconstateerd dat de relatie tussen de druk in het hoofd en de diameter lineair is. Dus bij een toename van de druk in het hoofd stijgt de diameter gelijkmatig mee.

In **hoofdstuk drie** beschrijven we een onderzoek waarin deze studie uit 1997 van de Duitse grondleggers van de techniek is gecombineerd met onze resultaten uit hoofdstuk twee. De resultaten suggereren dat het weefsel waaruit de schede rond de oogzenuw is opgebouwd, door hogere drukken zodanig wordt opgerekt dat de elasticiteit van de schede verandert. Dus dat het weefsel overrekt wordt en daardoor beschadigd raakt en minder elastisch wordt. Dit betekent dat we voorzichtig moeten zijn met de interpretatie van de resultaten bij patiënten waarbij de druk in het hoofd erg hoog is of is geweest. Dit betekent tegelijkertijd dat de diameters die gemeten worden bij mensen zónder chronisch verhoogde drukken in het hoofd wel lineair en meer betrouwbaar zijn als deze methode wordt gebruikt om bepaalde drukverhogende interventies te evalueren. Een beperking is echter dat de elasticiteit van de schede niet bij iedereen gelijk is, met name door verschillen in de steunweefsels waar de schede voor een deel uit is opgebouwd. We zullen dus altijd een uitgangsmeting (benchmark) moeten verrichten onder normale omstandigheden om de metingen tijdens een interventie te kunnen interpreteren.

De eerste interventie die we beschrijven is het plaatsen van een endotracheale tube (beademingsbuis) onder algehele anesthesie. Om de ademhaling gecontroleerd over te kunnen nemen worden patiënten met ernstig hersenletsel op de plaats van het ongeval onder narcose gebracht en wordt de eerder genoemde tube in de luchtpijp geplaatst. In **hoofdstuk vier** beschrijven we een onderzoek waarin we hebben gekeken of het plaatsen van een beademingsbuis tussen de stembanden in de luchtpijp een verhoging geeft van de druk in het hoofd. Daarnaast hebben we ook gekeken of het toevoegen van een extra pijnstiller aan de standaard narcosemiddelen deze reactie kan beperken. Dit onderzoek is uitgevoerd in de gecontroleerde omgeving van de operatiekamer bij mensen die bij een reguliere operatie onder anesthesie zijn gebracht en een beademingsbuis hebben gekregen. Uit dit onderzoek blijkt dat het plaatsen van een beademingsbuis zelfs na de toediening van narcosemiddelen de druk in het hoofd doet toenemen. Ook nadat de plaatsing gelukt is en de buis tussen de stembanden ligt, blijft de druk in het hoofd verhoogd. Het toevoegen van de extra pijnstiller lidocaïne aan de narcosemiddelen vermindert de reactie tijdens het plaatsen van de buis en zorgt dat de druk in het hoofd na tien minuten weer genormaliseerd is, ook tijdens de aanwezigheid van de buis tussen de stembanden. Dit onderzoek is uitgevoerd bij mensen zonder hersenletsel maar doet een gunstig effect vermoeden bij patiënten mét hersenletsel. Wij verwachten dat het toevoegen van lidocaïne aan de standaard narcosemiddelen een gunstig effect kan hebben op de doorbloeding van de hersenen na het plaatsen van een beademingsbuis bij traumapatiënten.

Verder viel op dat het intuberen op zichzelf een sterke prikkel is en een piek veroorzaakt in de hersendruk. Dit doet vermoeden dat het verstandig is om te voorkomen dat meerdere pogingen moeten worden ondernomen om de beademingsbuis te plaatsen nadat de narcose is toegediend. Meerdere pogingen zouden kunnen leiden tot meerdere pieken waarin de doorbloeding van de hersenen herhaaldelijk bedreigd raakt.

Om adequaat en in één keer een beademingsbuis te plaatsen is oefening en ervaring nodig. Traditioneel wordt hiervoor een instrument (Macintosh laryngoscoop) gebruikt waarmee de stembanden in de keel in beeld gebracht kunnen worden. Sinds enkele jaren zijn er instrumenten op de markt die aan het uiteinde een camera hebben waarmee de stembanden makkelijker op een scherm in beeld te brengen zijn. De verwachting is dat dit het intuberen van patiënten vergemakkelijkt.

In **hoofdstuk vijf** beschrijven we een vergelijking van de percentages van succesvolle intubaties van ambulanceverpleegkundigen, MMT-verpleegkundigen en MMT-artsen met de traditionele en met de videolaryngoscoop in de prehospitale zorg. We zien in deze vergelijking dat ambulanceverpleegkundigen met de videolaryngoscoop vaker in één poging correct intuberen dan met de traditionele laryngoscoop en dat het algehele succes van het luchtwegmanagement met een videolaryngoscoop groter is. De MMT-verpleegkundigen intuberen, vergeleken met de ambulanceverpleegkundigen, vaker in één poging goed, zowel met de traditionele als met de videolaryngoscoop. Vermoedelijk komt dit doordat MMT-verpleegkundigen op jaarbasis meer intubaties uitvoeren dan ambulanceverpleegkundigen en mogelijk ook doordat deze intubaties altijd onder supervisie van de aanwezige MMT-arts zijn uitgevoerd. Voor de groep ambulanceverpleegkundigen geldt dat een deel van hun intubaties zonder supervisie van een MMT-arts zijn uitgevoerd. In de groep van MMT-artsen was het totaal aantal succesvolle intubaties in één poging het hoogst. In deze groep maakte het geen verschil of er werd geïntubeerd met een traditionele- of een videolaryngoscoop. Dit komt naar verwachting doordat MMT-artsen meer ervaring hebben in intuberen gedurende hun loopbaan, maar ook doordat MMT-artsen per jaar meer dan vijftig intubaties uitvoeren waardoor de handeling een routine handeling is geworden.

In **hoofdstuk zes** beschrijven we een literatuurstudie die we hebben gedaan om te achterhalen hoeveel ervaring iemand moet hebben met het intuberen om een succespercentage van 90% te halen met een traditionele laryngoscoop. Onder optimale omstandigheden op een operatiekamer blijkt dat iemand die leert intuberen 90% van de patiënten in twee pogingen geïntubeerd krijgt na gemiddeld vijftig intubaties. Dat zou suggereren dat ambulanceverpleegkundigen in hun opleiding minimaal 50 patiënten zouden moeten intuberen om in twee pogingen een 90% succesrate te behalen. De omstandigheden waarin ambulanceverpleegkundigen moeten intuberen tijdens hun werk buiten het ziekenhuis zijn echter niet optimaal. Het is zeer waarschijnlijk dat de leercurve onder deze omstandigheden nog langer zal zijn. Het gebruik van een videolaryngoscoop door ambulancepersoneel lijkt dus een verstandige keuze als intuberen de manier blijft van het zekeren van de luchtweg door ambulancepersoneel in de prehospitale situatie. Of dit instrument een kortere leercurve heeft dan de traditionele manier moet nog goed worden uitgezocht.

Nadat de luchtweg is gezekerd en de beademing is ingesteld kan de patiënt geïmmobiliseerd worden om verdere verslechtering van de letsels aan bijvoorbeeld het ruggenmerg te voorkomen. In veel cursusboeken en protocollen wordt voorgeschreven dat patiënten onder meer een starre halskraag om gelegd moeten krijgen zodat voorkomen kan worden dat eventueel aanwezig nekletsel verergert tijdens de hulpverlening of tijdens het transport naar een ziekenhuis. Een halskraag heeft echter bijkomende effecten die patiënten met hersenletsel mogelijk verder in de problemen kunnen brengen. Als de kraag is aangebracht zoals wordt voorgeschreven in de gebruiksaanwijzing, ontstaat er een zekere mate van druk op de bloedvaten in de hals. Deze druk is onvoldoende om de slagaders dicht te drukken, maar kan wel de afvoerende vaten samendrukken die het bloed vanuit het hoofd terug naar het hart leiden. Hierdoor kan het zuurstofarme bloed in het hoofd opstuwen en daardoor de druk in het hoofd verder verhogen. In **hoofdstuk zeven** beschrijven we een studie waarin we bij 45 vrijwilligers zonder hersenletsel de schede rond de oogzenuw hebben opgemeten, zowel met als zonder halskraag. In dit onderzoek zien we dat de kraag bij iedereen een verbreding van de schede tot gevolg heeft en dat er dus zeer waarschijnlijk een verhoging van de druk in het hoofd ontstaat door het gebruik van een halskraag. Bij mensen zonder hersenletsel waarbij de druk in het hoofd niet verhoogd is zal deze toename geen gevaar vormen voor de doorbloeding van de hersenen. Bij mensen waarbij de druk na een ongeval wel verhoogd is, kan het omleggen van een kraag in theorie de doorbloeding van de hersenen wél negatief beïnvloeden. Gelukkig heeft de Nederlandse ambulancezorg het gebruik van de halskraag bij bewusteloze patiënten uit de protocollen geschrapt. Patiënten worden in een vacuümmatras of op een wervelplank geïmmobiliseerd alvorens op transport te gaan naar een ziekenhuis. Wetenschappelijk onderzoek heeft aangetoond dat patiënten met en zonder een halskraag even goed geïmmobiliseerd zijn en dat de halskraag dus niets bijdraagt bij de immobilisatie van een patiënt in een vacuümmatras of op een wervelplank.

Patiënten met tekenen van ernstig hersenletsel moeten primair naar een level 1 traumacentrum gebracht worden omdat daar 24 uur per dag een neurochirurg en een neuro intensive care aanwezig is. Nederland telt momenteel elf level 1 traumacentra, verspreid over het land. In sommige situaties kan het transport over de weg met een ambulance teveel tijd in beslag nemen en kan ervoor gekozen worden om de patiënt per helikopter te vervoeren. In **hoofdstuk acht** beschrijven we een onderzoek naar de effecten van het transport per helikopter op de hersendruk. Patiënten worden in rugligging, met hun hoofd in de vliegrichting gepositioneerd zodat de MMT arts in de buurt van het hoofd en het bovenlichaam van de patiënt zit. De benen van de patiënt liggen in het verlaagde compartiment onder de motoren in de richting van de staart van de helikopter. De rotorbladen van de helikopter duwen zich in de lucht omhoog om los te komen van de grond. Om voorwaarts te vliegen moet de piloot de helikopter voorover laten duiken met de neus iets naar beneden zodat de rotorbladen de helikopter niet alleen omhoog duwen maar ook in voorwaartse richting. Hierdoor komt de patiënt in een helling te liggen met het hoofd naar beneden. Het zuurstofarme bloed dat normaal passief terug naar het hart loopt, wordt nu het hoofd in gestuwd waardoor de druk in het hoofd in theorie toe zal nemen.

In ons onderzoek, met collega's als proefpersoon, zien we dat tijdens het opstijgen en vliegen in de helikopter de schede rond de oogzenuw inderdaad breder wordt tijdens de vlucht. In dit geval gaat het om een onderzoek bij mensen zonder hersenletsel. Als we de hoofdsteun van de brancard een beetje omhoog zetten, waardoor het bovenlichaam van de proefpersoon wat omhoog ligt en hetzelfde onderzoek herhalen tijdens een nieuwe vlucht, verbreedt de schede niet. Hieruit kunnen we concluderen dat het omhoog zetten van de hoofdsteun van de brancard voor, tijdens en na het helikopter transport zou kunnen voorkomen dat de druk in het hoofd tijdens het vliegen toeneemt.

Het alternatief voor een helikopter transport, is het vervoer over de weg per ambulance. In Nederland wordt vanwege de relatief korte afstanden vaker voor deze vervoerswijze gekozen. In **hoofdstuk negen** beschrijven we de effecten van een noodstop met een rijdende ambulance op de druk in het hoofd. Ook in een ambulance ligt de patiënt met het hoofd in de rijrichting. De patiënt ligt na een trauma geïmmobiliseerd in een vacuüm matras of op een wervelplank in rugligging. Als een ambulance een noodstop moet maken zal in theorie het bloed het hoofd in gestuwd worden. Dit zou er toe kunnen leiden dat de druk in het hoofd tijdens die noodstop toeneemt. In deze studie zien we dat de noodstop daadwerkelijk leidt tot een 24% verbreding van de schede rond de oogzenuw in de vrijwilligers. Als we dezelfde proef herhalen met de hoofdsteun dertig graden omhoog is het effect verdwenen. Dit zou betekenen dat het vervoeren van mensen met hersenletsel het beste in half zittende houding kan worden uitgevoerd. Dit kan natuurlijk alleen als de bloeddruk hoog genoeg is om in deze houding tegen deze helling op te kunnen stromen om de hersenen te doorbloeden. Deze interventie is heel gebruikelijk op een neuro intensive care maar werd tot voor kort nog niet in de pre-hospitale setting toegepast.

Het echoscopisch opmeten van de schede rond de oogzenuw door het gesloten ooglid lijkt veelbelovend, maar de uitvoering lijkt toch minder makkelijk dan we hadden geconcludeerd uit eerder onderzoek. Ieder echo onderzoek is een dynamisch onderzoek dat tijdens de uitvoering geïnterpreteerd wordt door degene die het uitvoert. Met name de keuze van het stil te zetten van het beeld waarop de uiteindelijke meting zal worden verricht, kent een subjectiviteit van de onderzoeker. Dit bepaalt de doorsnede waarop de diameter kan worden opgemeten. Hierdoor kan het lastig zijn voor een andere onderzoeker om precies hetzelfde plaatje vast te leggen en dezelfde breedte te meten in eenzelfde patiënt. In **hoofdstuk zeven** is het ons opgevallen dat simultane metingen op beide ogen, door 2 verschillende onderzoekers in dezelfde vrijwilliger van elkaar afwijken. Dit zou in theorie kunnen komen doordat de schedes van beide ogen verschillen in uitgangswaarde (benchmark) of verschillen in elasticiteit of dat in de ene schede meer hersenvocht wordt geperst dan in de andere. Echter is uit eerder onderzoek gebleken dat de verbreding van de schede in dezelfde patiënt synchroon verloopt in beide ogen. Het is waarschijnlijker dat de onderzoekers iets verschilden in hun uitvoering van de techniek waardoor de metingen varieerden. Dit noemt men de inter-observer variability. Deze variabiliteit werd eerder beschreven door Ballentyne et al. Hij stelde vast dat de inter-observer variabiliteit voor ervaren echografisten onder ideale omstandigheden erg klein is. Het artikel waarin hij deze bevindingen beschrijft is vaak geciteerd in vrijwel alle onderzoeken waarin de schede met echo gemeten werd. Door onze eigen ervaringen met het opmeten, zoals omschreven in **hoofdstuk acht** maar ook door andere studies die niet in dit proefschrift zijn opgenomen, betwijfelen wij of de inter-observer variability voor deze meting inderdaad zo laag is als in de meeste literatuur wordt omschreven. In **hoofdstuk elf** beschrijven wij in een systematische evaluatie van de beschikbare literatuur de inter-observer variabiliteit in de geïncludeerde artikelen. Uit deze studie van de literatuur blijkt dat de inter-observer variabiliteit veel groter is dan werd gesuggereerd door Ballantyne. Op basis van deze studie hebben we moeten concluderen dat de kans op meetfouten met deze methode groter is dan aanvankelijk werd gedacht en dat de techniek verder onderzocht en gestandaardiseerd moet worden om de reproduceerbaarheid van de metingen te vergroten. Tot die tijd moeten de uitkomsten met deze kanttekening worden geïnterpreteerd.

Voor de onderzoeken in dit proefschrift geldt dat de resultaten zijn verkregen uit onderzoek dat is uitgevoerd in voor ons maximaal haalbare optimale onderzoeksopstellingen. De meeste gegevens zijn verkregen uit metingen door één en dezelfde echografist. Voor beide echografisten in **hoofdstuk acht** was het gemeten effect van de halskraag significant: alleen de absolute meetwaardes verschilden van elkaar.

Al met al beschrijft dit proefschrift een aantal aanpassingen in de handelingen die worden toegepast in de prehospitale zorg voor patiënten met hersenletsel. Hopelijk kunnen deze aanpassingen de zorg verbeteren en wellicht de uitkomst voor de patiënt op de korte- en of langere termijn positief beïnvloeden. Er zal echter nog veel onderzoek gedaan moeten worden naar de interventies en behandelstrategieën. Doordat in het acute moment, bij gebrek aan een CT scan op straat, niet veel informatie kan worden verkregen over het type letsel aan de hersenen, zal de behandeling altijd een soort 'black box' benadering zijn. De klinische symptomen die passen bij verhoogde hersendruk - zoals bewustzijnsveranderingen, bloeddrukveranderingen door verdrukking van de hersenstam, pupil verschil en het verloren gaan van de pupilreactie op licht - zullen de collega's van de ambulance en het MMT op het spoor moeten brengen van ernstig hersenletsel.

Meer (gerandomiseerd) prospectief onderzoek zal moeten worden gedaan om een duidelijker beeld te krijgen van de effecten van bijvoorbeeld de prehospitale intubatie op de overleving van patiënten. Een studie naar de meerwaarde van de videolaryngoscoop in de handen van collega's van de ambulance kan helderheid bieden of dit instrument daadwerkelijk betere intubatie successen geeft. Er kan onderzoek worden gedaan naar de wijze van transport van patiënten met acuut hersenletsel, in plaats van de gezonde proefpersonen zoals in onze studie. Om dergelijke onderzoeken mogelijk te maken is het noodzakelijk dat de MMT's en de verschillende ambulancediensten hun data beschikbaar stellen op uniforme wijze of zelfs samenbrengen in één landelijke database waardoor onderzoek makkelijker uitvoerbaar en betrouwbaarder wordt. Schaalvergroting in de prehospitale acute zorg zoals bij de politie eerder gebeurde kan de zorg verder uniformeren en beter structureren. Dit kan leiden tot beter wetenschappelijk onderzoek en uniformiteit in de uitvoering van de zorg met uiteindelijk een betere kwaliteit van zorg.

De kleinste verbeteringen in de gezamenlijke zorg voor patiënten met hersenletsel kan een grote impact hebben op de levens van patiënten, diens naasten en de maatschappij in zijn totaliteit. Met name doordat vooral jonge mensen worden getroffen door deze vaak chronisch verlopende aandoening en daardoor weggerukt worden uit het arbeidsproces door een levenslange zorgbehoefte.

Samenvatting

ERASMUS UNIVERSITY ROTTERDAM

PHD PORTFOLIO

Iscander Michael Maissan

Description	
Genral courses	
ESHCC - BKO (2017)	6.00
Erasmus MC - Biomedical English Writing (2018)	2.00
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2019)	1.50
Leadership course Erasmus Medical Center (2019)	6.00
Specific courses	
Advanced Hazmat Life Support (2015)	0.60
Airway training day Erasmus MC (2015)	0.30
Cannot Intubate Cannot Oxygenate course Erasmus MC (2017)	0.25
Basics in cardiosonography (2020)	1.50
Seminars and workshops	
Dutch Anaesthesia conference (2015)	0.30
HEMS NL conference (2015)	0.60
Nationaal nascholingscongres NVA (2015)	0.60
Dutch Anaesthesia conference (2016)	0.25
Resuscitation congres (2016)	0.60
Dutch Anaesthesia conference (2017)	0.60
Dutch Anaesthesia conference (2018)	0.60
Talisman (2021)	0.30
Resus NL Amsterdam (2019)	0.60

Presentations

I'm excellent (2019) ResusNL	3.00
Time is Brain (2019)	1.00
Scientific meeting SUG NVA (2019)	2.00
Dispatch center Rotterdam (2021)	2.00
Prehospital Bloodtransfusions (2021)	1.00
Prehospital Care for TBI patients in the Netherlands (2021)	1.00
Traumatic Circulatory Arrest (2021)	1.00
ECMO in ambulances (2021)	0.30
Prehospital ECPR (2021)	0.50

National and international conferneces

Social Media And Critical Care Dublin (2017)	
Social Media And Critical Care Sydney (2019)	1.20
The Big Sick Zermatt Switzerland (2019)	
The Big Sick Zermatt Switzerland (2022)	

Other

Graduation research project Timo de Jong (2017) prehosp. POCUS	1.00
Instructorsday ATLS (2018)	0.20
Training Eric Bokhorst; new HEMS doctor (2018)	3.00
Training Dinis reis Miranda; new HEMS doctor (2018)	3.00
Graduation research project de Ruiter (2018) intubation lurningcurve	1.00
Graduation research project Verbaan (2019) ONSD & Trendelenburg	1.00
Training Caspar Muller; new HEMS doctor (2020)	3.00
Graduation research project Niek Vianen (2020) prehosp. research NL	2.00
Graduation research project Rutger Hollestelle (2021) inter observer variability ONSD	1.00
Education curriculum and e-learning Ambulance Academy (2022)	10.00
Revision HEMS protocols (2022)	3.00

Lecturing

Refereeravond Urgentie geneeskunde (2015)	0.10
ECMO skillstraining (2021)	0.60
Polytrauma Rapid Echo-Evaluation Program (2015)	0.60
PHPLS provider course (2018)	0.60
Educational day HEMS Netherlands (2018)	2.00
European Trauma Course (2018)	1.20
DSATC 3 day course (2019)	1.50
PHPLS provider course (2020)	0.90
Skillsdag MMT (2020)	1.50
ATLS provider course (2021)	1.00
PHPLS provider course (2021)	0.90
MOET provider course (2021)	0.90
ATLS provider course (2021)	0.90
DSATC 4 day course (2021)	1.50
On-Scene ECMO educational program Lifeliner 2 (2021)	3.00
	------ +
Total EC	**81.00**

1.0 EC = 25-30 hours

List of publications:

1. **Maissan I**, van Lieshout E, de Jong T, van Vledder M, Houmes RJ, Hartog DD, Stolker RJ. The impact of video laryngoscopy on the first-pass success rate of prehospital endotracheal intubation in The Netherlands: a retrospective observational study. Eur J Trauma Emerg Surg. 2022 Oct;48(5):4205-4213. PMID: 35362731
2. Hollestelle RVA, Hansen D, Hoeks SE, van Meeteren NLU, Stolker RJ, **Maissan IM**. Observer Variability as a Determinant of Measurement Error of Ultrasonographic Measurements of the Optic Nerve Sheath Diameter: A Systematic Review. J Emerg Med. 2022 Aug;63(2):200-211. PMID: 36038435
3. Luchette M, Helmke K, **Maissan IM**, Hansen HC, Stolker RJ, Tasker RC, Akhondi-Asl A. Optic Nerve Sheath Viscoelastic Properties: Re-Examination of Biomechanical Behavior and Clinical Implications. Neurocrit Care. 2022 Aug;37(1):184-189. PMID: 35237919
4. Vianen NJ, Van Lieshout EMM, **Maissan IM**, Bramer WM, Hartog DD, Verhofstad MHJ, Van Vledder MG. Prehospital traumatic cardiac arrest: a systematic review and meta-analysis. Eur J Trauma Emerg Surg. 2022 Aug;48(4):3357-3372. PMID: 35333932
5. **Maissan IM**, Vlottes B, Hoeks S, Bosch J, Stolker RJ, den Hartog D. Ambulance deceleration causes increased intra cranial pressure in supine position: a prospective observational prove of principle study. Scand J Trauma Resusc Emerg Med. 2021 Jun 30;29(1):87. PMID: 34193207
6. Ketelaars R, **Maissan IM**, Van't Leven W. Response to: Vitiello L, De Bernardo M and Rosa N. A-mode ultrasound evaluation of optic nerve in healthy volunteers to detect increased intracranial pressure after application of a rigid cervical collar. Eur J Emerg Med. 2020 Apr;27(2):149-150. PMID: 32101963
7. **Maissan IM**, Ketelaars R, Vlottes B, Hoeks SE, den Hartog D, Stolker RJ. Increase in intracranial pressure by application of a rigid cervical collar: a pilot study in healthy volunteers. Eur J Emerg Med. 2018 Dec;25(6):e24-e28. PMID: 28727580
8. **Maissan IM**, Verbaan LA, van den Berg M, Houmes RJ, Stolker RJ, den Hartog D. Helicopter Transportation Increases Intracranial Pressure: a Proof-of-Principle Study. Air Med J. 2018 Jul-Aug;37(4):249-252. PMID: 29935704
9. Klein Nulent CG, de Graaff HJ, Ketelaars R, Sewnaik A, **Maissan IM**. Anesthetic Management During Emergency Surgical Ligation for Carotid Blowout Syndrome. A A Case Rep. 2016 Aug 15;7(4):85-8. PMID: 27310900
10. **Maissan IM**, Hoeks SE. Response. J Neurosurg. 2016 Apr;124(4):1134. PMID: 27482579
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Dr. Lichtveld, beste Rob, soms kom je op een kruispunt dat bepalend kan zijn voor de rest van het leven. Eén van de belangrijkste kruispunten in mijn leven lag in 2001 in een portokabin in Utrecht waar je mijn bekwaamheidsverklaring hebt getoetst en getekend als ambulance chauffeur. Vanaf dat moment is voor mij een droom uitgekomen en mijn prehospitale carrière in de acute zorg begonnen die uiteindelijk geleid heeft tot dit proefschrift. Hartelijk dank voor de kansen die je mij hebt gegeven!

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Na je artsenexamen ging je mij voor naar de andere stoel in de ambulance in de rol van verpleegkundige. Anderhalf jaar later zat ik er ook. Jij begon als MMT arts en acht maanden later startte ik ook binnen dit mooie beroep. Vorig jaar mocht jij je proefschrift verdedigen en nu ben ik aan de beurt.

Net als broers, kunnen wij ook flink verschillen en kunnen de vonken er af spatten bij discussies. Maar: zonder wrijving geen glans en ieder conflict is een kans! In het ECMO project van Dinis hebben we elkaar weer helemaal teruggevonden.

Tot slot hoop ik dat je nog steeds elke vakantie restjes confetti vindt in je caravan ;-)

Kolonel Drs. Dirven, beste Perjan, deze wetenschappelijke reis is begonnen met één van jouw proefballonnetjes. Jouw tomeloze energie en enthousiasme hebben mij meegenomen in ons eerste turbulente wetenschappelijke avontuur. Je nam mij mee naar een echocursus om het echo apparaat te leren kennen. Het rendement van deze cursus was vele malen groter dan van tevoren verwacht. Daarover later meer.

Tijdens de echocursussen, die we daarna samen als instructeurs hebben gegeven, zijn weer nieuwe ideeën voor vervolgonderzoek geboren. Hartelijk dank aan jou maar ook aan **Isabelle Huig** en **Rein Ketelaars** voor de bron van inspiratie en het sparren over nieuwe onderzoeksvragen.

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Paranimfen. Something old, something new. Ik ben heel blij en vereerd dat jullie mij bij willen staan tijdens dit huwelijk met de academie.

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Curriculum vitae

Iscander Michael Maissan werd geboren op 20 februari 1978 te Leiden. Na het behalen van zijn VWO diploma in 1999 aan het Gouwe College in Gouda is hij Geneeskunde gaan studeren aan de Erasmus Universiteit te Rotterdam.

Tijdens de opleiding heeft hij van 2001-2002 gewerkt als chauffeur bij de huisartsenpost in Gouda. Daarna is hij gaan werken als ambulancechauffeur bij verschillende ambulancediensten in de regio Zuid West Nederland.

Deze prehospitale ervaring in de acute zorg heeft zijn interesse en toekomst perspectief gevormd. Tot het laatste moment van de co-schappen twijfelde hij over welke discipline het beste zou passen. De spoedeisende geneeskunde leek erg voor de hand te liggen maar was nog erg nieuw in Nederland. De huisartsengeneeskunde leek aantrekkelijk en voor de hand liggend omdat zijn vader op dat moment ook huisarts was. Het laatste co-schap bij de Anesthesiologie heeft de doorslag gegeven.

In 2007 werkte hij als ANIOS op de spoedeisende hulp van het Erasmus MC en vanaf 2008 startte hij met de opleiding tot Anesthesioloog onder supervisie van Prof. Dr. Jan Klein en vanaf 2009 onder Prof. Dr. Robert Jan Stolker.

Tijdens de opleiding tot Anesthesioloog is hij altijd op de ambulance blijven werken maar dan niet meer als chauffeur maar dan als basisarts op de stoel van de verpleegkundige. In deze periode heeft hij via verschillende uitzendbureaus bij tal van ambulancediensten gewerkt in Nederland.

Aan het einde van de opleiding tot Anesthesioloog heeft hij een verdiepingsstage van een half jaar gedaan in de Urgentie-Anesthesiologie en is in diezelfde tijd ingewerkt als MMT arts bij Lifeliner 2 in Rotterdam.

Vanaf september 2012 werkt hij als MMT arts bij het Mobiel Medisch Team van het Erasmus MC.

Gedurende de opleiding heeft hij bij tal van cursusaanbieders in de urgentie geneeskunde als instructeur gewerkt. Cursussen die hem en de cursisten voorbereidde in de zorg voor levensbedreigende omstandigheden bij kinderen, volwassenen, zwangere vrouwen en ouderen. Maar ook in het doen van snel en doelmatig onderzoek met echografie op de plaats van incident. Dit resulteerde in een academische basiskwalificatie in onderwijs van de afdeling onderwijs van het Erasmus MC.

Vanaf 2015 heeft hij een neventaak op zich genomen binnen het MMT als Coördinator Kwaliteit en Onderwijs. In deze functie verzorgt hij onderwijs aan (nieuwe) MMT artsen, onderwijs aan de Academie voor Ambulancezorg en onderwijs in de regio aan ketenpartners in de verschillende ziekenhuizen.