Continuous monitoring of $P_{br}O_2$ in patients with severe head injury

ISBN 90-9017868-6

Layout en printing: Datawyse / Universitaire Pers Maastricht

The publication of this thesis was financially supported by Medtronic, Sofamor Danek

Continuous monitoring of $P_{br}O_2$ in patients with severe head injury

Continue bewaking van de $P_{br}O_2$
bij patiënten met een ernstig schedelhersenletsel

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.S.W.J. Lamberts
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 10 maart 2004 om 11.45 uur.

door

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geboren te Eibergen

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Contents

Abbreviations

99m-TC HMPAO	99m Technetium HexaMethyl Propylene Amine Oxime
ABP	Arterial Blood Pressure
ATLS	Advanced Trauma Life Support
$AVDO_2$	Arterio Venous Difference in Oxygen
CBF	Cerebral Blood Flow
CBS	Centraal Bureau voor de Statistiek
CBV	Cerebral Blood Volume
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CPP	Cerebral Perfusion Pressure
CSF	CerebroSpinal Fluid
CT	Computer Tomogram
CVR	Cerebro Vascular Resistance
EBIC	European Brain Injury Consortium
FiO_2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
Hb	Hemoglobin
HFVS	High Flow Velocity State
ICA	Internal Carotid Artery
ICP	IntraCranial Pressure
ICU	Intensive Care Unit
IMV	Inspiratory Minute Volume
LFVS	Low Flow Velocity State
mABP	mean Arterial Blood Pressure
MCA	Middle Cerebral Artery
P_aCO_2	partial pressure of arterial Carbon diOxide
P_aO_2	partial pressure of arterial Oxygen
$P_{br}O_2$	partial pressure of brain tissue Oxygen
PCO_2	partial pressure of Carbon diOxide
PH	partial pressure of Hydrogen
PO_2	partial pressure of Oxygen
PI	Pulsatility Index
rCBF	relative Cerebral Blood Flow
RTA	Road Traffic Accident
SaO_2	arterial Oxygen Saturation
SIMV	Synchronized Intermittent Mandatory Ventilation
SjO_2	Jugular venous Oxygen Saturation
SPECT	Single Photon Emission Computed Tomography
std	standard deviation
TCD	Trans Cranial Doppler
TOR	Tissue Oxygen Response
TSAH	traumatic SubArachnoid Hemorrhage
USA	United States of America
Vica	Flow velocity in the internal carotid artery
Vmca	Flow velocity in the middle cerebral artery
Xe	Xenon

This thesis is based on the following publications

1. Continuous monitoring of brain tissue PO_2 after severe head injury. *H van Santbrink*, AIR Maas, CJJ Avezaat. In: H Nagai, K Kamiya, S Ishii (eds), Intra Cranial Pressure Vol. IX, Springer Verlag Berlin, Heidelberg, New York, Tokyo, 582-584
2. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *H van Santbrink*, AIR Maas, CJJ Avezaat. Neurosurgery 38(1): 23-33,1996
3. Brain oxygen tension in severe head injury. WA van den Brink, *H van Santbrink*, EW Steyerberg, CJJ Avezaat, JA Carmona Suazo, Ch Hoogesteeger, WJ Jansen, LMH Kloos, J Vermeulen, AIR Maas. Neurosurgery 46(4): 868-878,2000
4. CO_2 reactivity and brain oxygen pressure monitoring in severe head injury. JA Carmona Suazo, AIR Maas, WA van den Brink, *H van Santbrink*, EW Steyerberg, CJJ Avezaat. Crit Care Med 28(9): 3268-3274,2000
5. Brain Tissue Oxygen Response in severe traumatic brain injury. *H van Santbrink*, WA van den Brink, EW Steyerberg, JA Carmona Suazo, CJJ Avezaat, AIR Maas. Acta Neurochirurgica 145: 429-438,2003
6. Brain tissue PO_2 validation by Single Photon Emission Computed Tomography. *H van Santbrink*, JW Schouten, CJJ Avezaat, EW Steyerberg, AIR Maas. In preparation for publication.
7. Serial Transcranial Doppler measurements in traumatic brain injury with special focus on the early posttraumatic period. *H van Santbrink*, JW Schouten, EW Steyerberg, AIR Maas, CJJ Avezaat. Acta Neurochirurgica 144(11): 11411149,2002

CHAPTER 1

General introduction to traumatic brain injury

H van Santbrink

1.1 Epidemiology

In the western world traumatic brain injury is a major health care problem. It remains the leading cause of death among young adults, though a slight reduction has been observed over the past years.
In the Netherlands 2,4 million people annually receive medical assistance for injuries. Nearly half of this population is below 25 years of age. Sports, work environment and road traffic accidents (RTA) accounts for the majority of injuries in this age group. Victims of RTA and accidents at work sustain more severe injuries than victims from injury of other causes. 37% of the injury victims is treated by only the general practitioner, 50% are treated in a hospital, and 4% require hospital admission.[1] Approximately one fifth of these hospital admissions is caused by RTA.[2] (table 1)

Table 1. Road traffic injuries and victims on the public road in the Netherlands.

	1994	1995	1996	1997	1998
Road traffic injuries					
With death	1191	1227	1099	1076	988
With hospital admission	17280	18000	17480	18100	-
Road traffic victims					
With death	1298	1334	1180	1163	1066
With injured with hospital admission	19840	20000	19420	20190	-

The annual financial burden in the Netherlands due to medical costs caused by injuries was calculated at $ 952 million, compared to $ 915 million for cancer and $ 1746 million for cardiovascular diseases.[3]

Head injury

In the United States of America (USA) about 1.5 million people sustain a traumatic brain injury and about 1 million people are treated and discharged from an emergency room for a traumatic brain injury each year. The incidence of head injuries requiring hospitalization is variable, due to differences in criteria for head injury and admission policy. Most estimates however are in the range of 200-300/100,000. The incidence of death due to traumatic brain injury is 10-15/100,000, varying according to geographical area with lower mortalities in the developed countries.[4,5] Approximately 1 out of every 4 adult patients with TBI is unable to return to work one year after injury. Recent studies in the Netherlands showed that 88/100,000 inhabitants require hospitalization for head injury with a total incidence of head injuries of 837/100,000. Approximately 1% of these patients concern a severe head injury, as defined by a Glasgow Coma Scale (GCS) score of 8 or less. A peak incidence in head injury victims is observed in the second and third decade, with a male predominance of 2:1.[6] (figure 1)

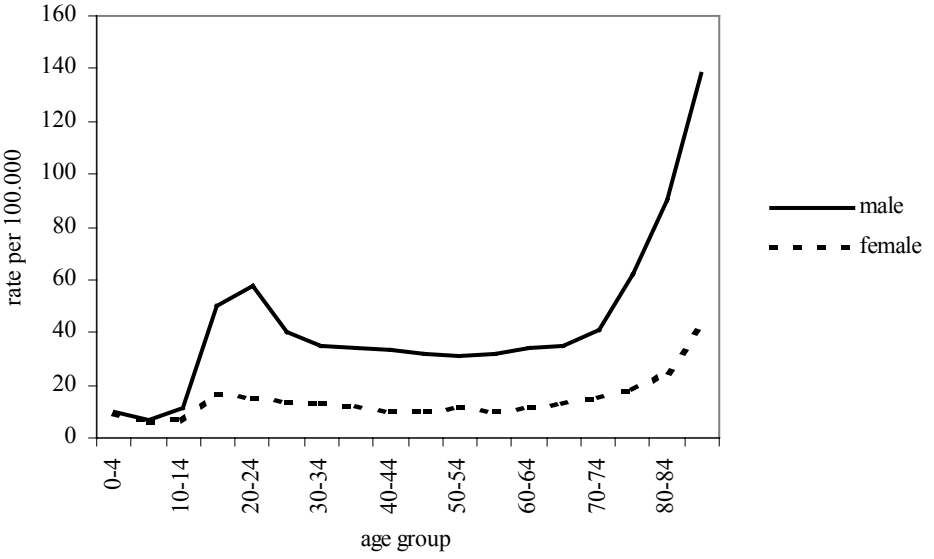

Figure 1. Traumatic brain injury-related death rates by age and gender, in the USA, 1994.[4]

Head injury in Rotterdam

The Erasmus Medical Center has a referral area that compromises about 1.8 million people. According to the hospital administration records an average of 250 patients are admitted each year with a head injury, and approximately half of these patients (52%) are admitted to an Intensive Care Unit (ICU). The overall mortality rate was 15%, and 16 % could not be discharged to their home environment.

1.2 Classification of head injury

Since the mid seventies the clinical severity of head injury is classified according to the Glasgow Coma Scale (GCS).[7] On this scale three aspects of responsiveness are scored: eye opening, motor response of the upper extremities to commands or painful stimuli and verbal reaction.(table 2) For application in individual patients the 3 sub scores of the GCS should be reported separately, but for purposes of classification and research, the scores of the sub scales can be added, yielding a minimal total score of 3 and a maximum of 15. According to this scale head injuries are classified in mild (GCS 14-15), moderate (GCS 9-12) and severe (GCS 3-8). The scale has been tested for interobserver agreement and proved reliable.[8]

Table 2. Glasgow Coma Scale (GCS).

Eye opening	spontaneously	4
	to verbal command	3
	to pain	2
	no response	1
Verbal response	oriented	5
	confused conversation	4
	inappropriate words	3
	incomprehensible sounds	2
	no response	1
Motor response	obeys commands	6
	localizing	5
	flexion withdrawal	4
	abnormal flexion	3
	extension	2
	no response	1
Total		3-15

Introduction of computerized tomography scanning (CT) of the head has greatly improved diagnostic facilities and further provided opportunities for a more morphological classification. The CT classification according to Marshall [9] or modifications of this classification is widely used in neurotraumatology studies and ads important prognostic information to clinical parameters.(table 3)
Outcome after head injury is generally classified according to the Glasgow Outcome Scale (GOS).[10] This scale is a simple scale for assessing overall outcome after head injury. The scale is for practical purposes sometimes dichotomized into 2 groups: Unfavorable; Dead, vegetative and severely disabled and Favorable; Moderately disabled and good recovery. (table 4) International

Table 3. Diagnostic categories of types of abnormalities visualized on CT scanning.

Category	Definition
Diffuse injury I	no visible intracranial pathology seen on CT scan
Diffuse injury II	cisterns are present with midline shift 0-5 mm and/or: lesion densities present, no high or mixed-density lesion > 25 cc, may include bone fragments and foreign bodies
Diffuse injury III	cisterns compressed or absent with midline shift 0-5mm, no high or mixed-density lesion > 25 cc
Diffuse injury IV	midline shift > 5mm, no high or mixed-density lesion > 25 cc
Evacuated mass lesion	any lesion surgically evacuated
Nonevacuated mass lesion	high or mixed-density lesion > 25 cc, not surgically evacuated

According to Marshall LF et al.[9]

acceptance of scaling has facilitated comparison between different studies, although some differences may result from observer variability in interpretation of the patients condition.[11] This observer variability may be diminished by the use of the structured interview for assessing the GOS.[12]

Table 4. Glasgow Outcome Scale (GOS).

Dead	1
Vegetative	2
Severely disabled	3
Moderately disabled	4
Good recovery	5

1.3 Treatment of head injury

Final outcome after traumatic brain injury is determined by the additional effects of the so-called primary and secondary injury.
Primary injury consists of damage that occurs on the scene of the accident and therefore is in itself non-treatable, only preventable. Introduction of seat belts and air bags in cars, obligatory fall-helmets and improvement of the safety of cars in general contributed to the decrease in the number of severely injured RTA victims.
Secondary damage evolves over the time after the accident. The injured brain is extremely sensitive to alterations in body homeostasis during the period after injury.

Table 5. Systemic and intracranial secondary insults to the brain.

Systemic secondary insults
Hypoxia
Hypotension
Hypercapnia
Hypocapnia
Hyperthermia
Hyperglycemia
Hypoglycemia
Hyponatremia
Hypoproteinemia
Anemia
Intracranial secondary insults
Intracranial hypertension (hematoma, edema, contusions, hydrocephalus, vascular engorgement)
Seizures
Vasospasm
Infection

Adapted from Teasdale [46] and Maas [47]

Disruptions of body homeostasis are called secondary insults, these can arise from systemic/extracranial and/or intracranial origin.(table 5)
Treatment of head injury is mainly based on early prevention, recognition, and aggressive treatment of these secondary insults. The final common pathway leading to deterioration following secondary insults is ischemia. Treatment according to fixed protocols, from the first moment on the scene of the accident till discharge from the hospital, seems mandatory in preventing secondary insults as much as possible. Guidelines for the management of TBI have been developed both in the USA and in Europe.[13,14]

1.3.1 Regulation of Cerebral Blood Flow

Under normal conditions Cerebral Blood Flow (CBF) is kept within certain limits by various regulating mechanisms.

A. Metabolic coupling

CBF in normal conditions is strongly related to the metabolic activity of the brain. The CBF is regulated by arteriolae, which can dilate or constrict. The exact mechanism is not clear.[15,16]

B. Autoregulation (blood pressure regulation)

The mechanism of autoregulation maintains CBF at relatively constant levels, despite variations in mean arterial blood pressure (mABP). Between mABP values of 50 to 150 mmHg CBF is kept constant by variations in Cerebro Vascular Resistance (CVR), by vasoconstriction or –dilation of the arteriolae. Longstanding alterations in mABP can shift the limits of autoregulation. In case of hypertension the limits of autoregulation are shifted upwards, which is probably caused by adaptation of the arteriolar walls.[17,18,19]

C. CO_2 reactivity

CO_2 reactivity mechanisms in the brain respond to alterations in arterial PCO_2 and PH. Decrease of the arterial PCO_2 causes vasoconstriction in the arteriolae and thus a reduction in CBF. In normal conditions a reduction of 4-8% in CBF is achieved by a reduction of 1 mmHg in arterial PCO_2.[20,21] Hyperventilation in case of raised Intracranial Pressure(ICP) is based on this theory. By decreasing P_aCO_2, Cerebral Blood Volume (CBV) is reduced, and thus ICP.

D. Tissue Oxygen Response(TOR)

O_2 reactive mechanisms in the brain have been known for a long time. Kety and Schmidt showed that in healthy volunteer's CBF changes markedly in relation to changes in arterial O_2 content. Reduction of CBF with an average of 13% was achieved by inhalation of high oxygen mixtures (85% and 100% fraction of inspired oxygen (FiO_2)). Hypoxia, by respiration of gas mixtures of 10% O_2 induced an

average increase in CBF of 35%. Other studies have confirmed these observations. Again, cerebral resistance vessels that are sensitive to alterations in arterial PO_2 probably regulate CBF.[21,22,23,24]

1.3.2 Monitoring of patients with severe head injury

Patients with a severe head injury (GCS≤ 8) are in general admitted to an ICU and artificially ventilated. Clinical condition and sedation are responsible for the fact that repeated physical examination is insufficient to detect impending clinical deterioration and therefore additional monitoring parameters are applied in the ICU setting. Monitoring the severely head injured patient is directed at early recognition of secondary insults. Since ischemia is considered to be the final common pathway of these insults, monitoring is directed towards impending ischemic insults. All monitoring parameters are therefore more or less related to CBF.

A. mean Arterial Blood Pressure(mABP)

In most cases one of the peripheral arteries is cannulated (radial artery, femoral artery) and invasive blood pressure can be measured directly. An advantage of direct cannulation of one of these arteries is the possibility to measure blood gasses in a simple way by withdrawing a blood sample. Mean ABP should be kept at least above the lower limit of autoregulation to secure an adequate CBF.

B. Intracranial Pressure Monitoring(ICP)

ICP has been measured in head injured patients since the sixties/seventies. [25] The assumption underlying measurement of ICP in one region of the cranial cavity is that this cranial cavity consists of one compartment filled with a non-compressible substance. Nevertheless, pressure gradients have been reported. The intracranial content consists of three components, brain tissue, Cerebrospinal Fluid (CSF) and blood. If one of these components increases in volume, ICP can initially be kept within relatively normal limits, by reduction of volume in one of the other compartments. If the volume increase exceeds compensatory mechanisms, only a small increase in volume of one of the compartments will induce a large ICP increase (Kelly Monroe doctrine). Normal ICP is below 10-15 mmHg. The gold standard to measure ICP is to measure the CSF pressure in the ventricular system. Cannulation of one of the ventricles is therefore considered the most accurate way of measuring ICP and provides additionally the opportunity to drain CSF in order to reduce ICP. Incidence of infection of a ventricular catheter is 5-10%, and increases whith monitoring time, particularly when this exceeds 5 days.[26]
Modern technologies provide other ways for measuring ICP. Intraparenchymal, subdural and intraventricular sensors with microtechnology offer a more easy way to measure ICP, but recalibration after insertion is generally not possible, thus adversely influencing reliability.[27,28,29]
Raised ICP after head injury is associated with more unfavorable outcome. In almost half of the patients who die after a severe head injury, raised ICP is the

primary cause of death.[30] Practice recommendations strongly advise treatment of raised ICP.

C. Cerebral Perfusion Pressure(CPP)

Cerebral Perfusion Pressure (CPP) is defined as mABP – mean ICP. Normally CPP is between 60 and 80 mmHg. The cutoff point at which regulatory mechanisms fail to maintain CBF within normal ranges differs per patient. Reduction of CPP below this cutoff point, especially in patients with a severe head injury, will cause a reduction in CBF. It is generaly thought that a CPP of 60-70 mmHg should be sufficient to maintain CBF at normal levels. Reduction of CPP below this level will result in reduction of CBF with increased risk of ischemia.[31] CPP may be reduced by either a decrease in mABP or an increase in ICP, or by a combination of these two mechanisms.[32,33]

D. Jugular bulb oxymetry(SjO_2)

Continuous measurement of the venous oxygen saturation in the jugular bulb (SjO_2) can provide online information on cerebral oxygen metabolism. A catheter with a reflection spectrophotometric oximeter is introduced into the internal jugular vein, and advanced until the tip of the catheter reaches the base of the skull. The position of the catheter tip should always be controlled with a lateral X-ray of the cranio-cervical region, demonstrating a position above the lower border of the first cervical vertebra.[34,35] Below the level of C1 blood in the jugular vein is a mixture of cerebral and extracerebral origin and misleading high SjO_2 levels may be obtained. Measurements of the arterio - jugular venous difference in oxygen content ($AVDO_2$) provides information on the relationship between global cerebral metabolic rate of oxygen ($CMRO_2$) and CBF, according to the Fick principle. $AVDO_2 = CMRO_2/CBF$. $AVDO_2$ is calculated as: hemoglobin (Hb) concentration x 1.39 x arterio-venous oxygen saturation. Since Hb, arterial oxygen saturation and the position of the Hb dissociation curve remain relatively constant over short time intervals, the SjO_2 is proportional to the $CBF/CMRO_2$. Under normal circumstances CBF and $CMRO_2$ are coupled and the ratio of these parameters remains constant, without any change in SjO_2. Coupling between CBF and $CMRO_2$ in patients with severe head injury is disturbed in over half of the cases.[36] If oxygen supply to the brain, e.g. CBF, decreases an increased oxygen extraction, $AVDO_2$, and thus a reduction of SjO_2 will occur. Normal values for $AVDO_2$ are around 7 ml O_2/100ml blood and normal SjO_2 values between 55-75%.[37] Higher values represent increased oxygen extraction due to insufficient perfusion and indicate global ischemia. Low $AVDO_2$ levels or high SjO_2 levels indicate hyperemia. No distinction can be made between absolute and relative hyperemia, in both circumstances CBF is elevated relative to cerebral metabolic requirements. In case of absolute hyperemia CBF is above 50 ml/100mg/min, with a normal or decreased $CMRO_2$, in case of relative hyperemia CBF may still be normal but $CMRO_2$ is decreased.[38] The different conditions are represented in figure 2.

Measurement of SjO_2 provides information about the global cerebral oxygen metabolism. Focal disturbances can be missed with this technique, since the jugular oxygen saturation represents the mean of the whole hemisphere. Regional ischemia may be compensated by hyperemia in other parts. In case of brain death, misleading high SjO_2 values may be obtained, as no cerebral extraction of oxygen occurs.

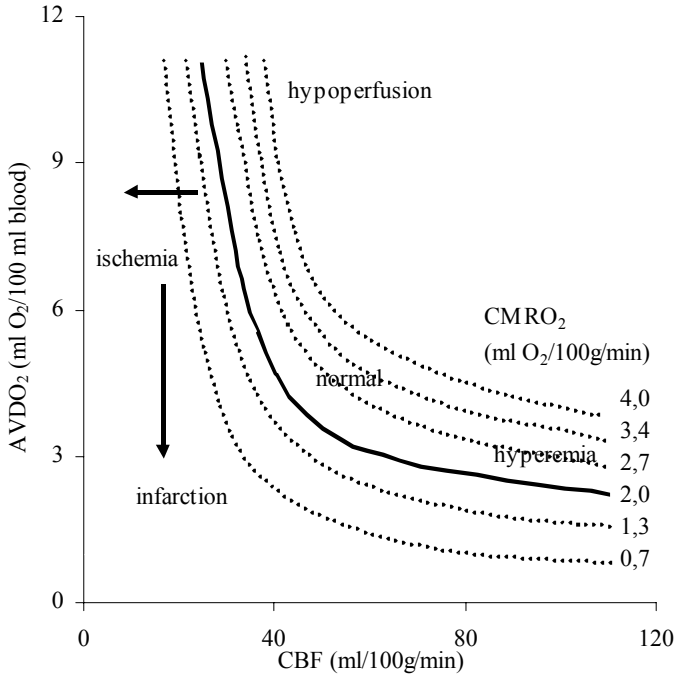

Figure 2. Relationship between cerebral metabolism and CBF in comatose patients. In absence of cerebral ischemia, the AVDO2 and CBF have the relationship illustrated by the solid curve, with a CMRO2 averaging 2,3 ml/100g/min. In case of ischemia/infarction the relationship changes. (adapted from Robertson CS, et al.[38])

Discussion exists as to which jugular vein should be canulated. In general, the right jugular vein is dominant and drains most supratentorial venous blood. A simple compression test of a unilateral jugular vein can elucidate which jugular vein is dominant. The side with the most prominent ICP rise is the dominant side and be chosen for optimal SjO_2 monitoring.[34,35,37]

A continuous spectrophotometric jugular bulb oximeter requires an in vivo calibration every 8 – 12 hours, as catheter accuracy may change. Calibration is performed against analysis of blood samples from the jugular catheter. Further, every acute change in SjO_2 reading should be checked with an accuracy calibration procedure. Initial experience in the use of these catheters showed unreliable recordings in half of the cases, mostly due to a poor catheter position.[39] Later studies showed an improved performance reflecting improvements in catheter

technique, immobilization of the patient with a stiff cervical collar and a constant learning curve.[40]

1.3.3 Treatment protocol for patients with severe head injury

Treatment of patients with a severe head injury is directed towards prevention, early recognition and treatment of secondary insults. Because the complexity of the problems which the clinician encounters treatment is guided by protocols, starting with the protocol of the Advanced Trauma Life Support (ATLS). This protocol is based on the adagium "treat first what kills first", and pays special attention to the ABC's; Airway, Breathing and Circulation.[41] These principles are very relevant to patients with a severe head injury since the traumatized brain demonstrates increased vulnerability to hypoxia and hypotension. In addition to this general principles, specialized protocols have been developed for the brain injured patient.[13,14,42,43,44,45]

1.3.4 Occurrence of ischemia after severe head injury

The incidence of cerebral ischemia after severe head injury is high. Postmortem studies in patients with a fatal head injury report an incidence up to 90%[46,47], even when ischemic changes due to tentorial herniation are excluded. Ischemic changes are mainly focal with a prediliction for the arterial boundary zones. It may be concluded that these observations resulted from a critical reduction in CBF. In most of the cases with postmortem ischemic changes, ICP was above normal and in about 30% systolic blood pressure was below 80 mmHg.
Further studies showed the relevance of a raised ICP as a severe secondary insult. The incidence of raised ICP, defined as an ICP > 20 mmHg during 5 minutes or more, after a severe head injury is 55-75%. Patients with a raised ICP have a mortality of 44%, in contrast to patients without a raised ICP who have a mortality of only 8%.[30,48] Up to 50% of the patients with a fatal head injury died due to uncontrollable ICP.[49] Other studies show a strong association between CT scan appearance and mortality. Also patients with radiologic signs of raised ICP, e.g. compressed basic cisterns, fair more poorly. Patients without visible pathology on the admission CT scan have an overall mortality of 9,6% and patients with shift, or an evacuated or non-evacuated mass lesion on the admission CT scan have an overall mortality of 38,8-56,2%.[50] If the primary attention after severe head injury is directed towards CPP instead of ICP management, the same tendency is observed. Rosner showed in his series that 40% of the head injured patients needed supportive vasopressive therapy to maintain adequate CPP. Mortality in this group was 47% versus 18% in patients who did not need any vasopressive therapy.[33]
Raised ICP or a decreased CPP, with a subsequent expected decrease in CBF is according to these data a very common finding after severe head injury and negatively correlated to good outcome.
According to data obtained with jugular bulb oxymetry, secondary ischemic insults occur in 30-40 % of the patients. Ischemic insults are defined as SjO_2 saturation < 50-55% during a period of 10 minutes or more. These episodes of desaturation are

most common during the first day after trauma (37% of the episodes) and are associated with a reduced CBF and a poor prognosis.[51,52,53,54,] To the contrary, measurements of CBF beyond the first period after trauma show a relative low frequency of ischemia and a high frequency of hyperemia.[36] In nearly half of the cases SjO_2 desaturation periods were caused by an elevated ICP or decreased CPP, and systemic causes as hypocarbia and hypotension.[39] Treatment directed towards increasing CBF, mainly by fluid resuscitation, reduces the number and length of periods of SjO_2 desaturation.[54] If high $AVDO_2$ levels do not respond immediately to therapy, as hematoma evacuation or administration of mannitol, this is associated with an unfavorable outcome and a high incidence (43%) of radiologically diagnosed delayed cerebral infarction.[55]

Interpretation of SjO_2 measurements has not only technical, but also physiological limitations. The relation between SjO_2 and CBF only exists when $CMRO_2$ remains constant. $CMRO_2$ can vary depending on the time after injury, in most cases $CMRO_2$ is reduced in the initial period after injury. One can speak of a "compensated hypoperfusion" in case of a reduced CBF in combination with a reduced $CMRO_2$, which is expressed by a low level of lactate and a high $AVDO_2$. In case of real ischemia with an elevated lactate level, CBF is not adequately represented by the $AVDO_2$.[38] In this situation CBF decreases more than the increase in $AVDO_2$ supposes. Besides local or regional ischemia can be missed by SjO_2 measurements alone, since it represents the mean hemispheric oxygen extraction.

Several papers reported on serial Trans Cranial Doppler (TCD) studies in head injured patients. The Flow velocity that is measured with TCD, is proportional to the volume of CBF and inversely related to the cross-sectional area of the insonated vessel. Usually the middle cerebral artery (MCA) and the extracranial internal carotid artery (ICA) are insonated and time course of flow velocity in these vessels is studied.

During the initial period after injury low values are observed, probably due to a reduced CBF. The incidence of a low mean blood flow velocity varies from 45%-56%. Initial low flow velocity values are related to the severity of injury and finally to outcome 6 months after injury.[56,57,58,59]

Vasospasm can be one of the mechanisms after severe head injury that induces secondary ischemic insults. Increased blood flow velocity may occur in association with elevated CBF or reduced vessel diameter (vasospasm). Mild vasospasm is defined as a flow velocity in the MCA > 100 cm/s, and severe vasospasm as a flow velocity > 200 cm/s. To discriminate between vasospasm and an increased CBF additional information can be obtained by calculating the ratio between flow velocity in the MCA and ICA, known as the Lindegaard index. A value > 3 represents vasospasm in the MCA. Spastic flow velocity values in the MCA are observed round day 2-7 after injury, with a median duration of 4 days. The observed incidence of spastic flow velocity values is up to 27%-40%. The incidence of vasospastic values is positively associated with the amount of traumatic SubArachnoid Hemorrhage (tSAH) or intracerebral blood seen on the CT scan, and with the occurrence of noncontusion related infarction seen on late CT scans.[57,60,61,62,63,64] Only a few studies confirmed spastic flow velocity values

with angiography or CBF studies in head injured patients. The association between high posttraumatic flow velocity values and outcome remains debatable.[58,59,63,65]
CBF studies are not routinely performed in the management of head injury. Time, costs, technical considerations and the fact that they only provide a single point measurement limit practical application. Normal CBF values are between 35-50 ml/100g/min. Cellular dysfunction starts at a level below 20-23 ml/100g/min and irreversible ischemic changes occur at flow levels below 10-18 ml/100g/min. A combination of duration and depth of the reduced CBF finally causes ischemia and cellular death. The penumbra zone is defined as a zone in which neuronal electrical dysfunction occurs, but oxygen supply is still sufficient to maintain cellular wall integrity and the cell will remain viable, at CBF ranges between 10-20 ml/100g/min. If CBF can be returned to normal levels, the cell function can be restored.[66,67,68,69,70,71]
Initial CBF studies in patients with a head injury showed a clear relation between CBF and time after injury. These studies showed low CBF values within the first 24 hours after injury, increasing towards hyperemic values after this period, although a wide variation in CBF values was noted between the different study groups. The hyperemic phase could last up to several weeks after trauma. Initial low CBF values were correlated with poorer outcome and strongly correlated to mortaliy at initial CBF value, < 20 ml/100g/min. During this initial time period after injury, autoregulation was disturbed in all patients tested. No conclusion can be drawn in respect towards the frequency of early ischemia in this study because of sampling bias.[72]
These findings were confirmed by Obrist et al.[36] who performed serial CBF measurements in 75 patients. First measurements in this study were performed within 96 hours after trauma. In 45% of the patients a CBF below the normal value was found. Though these patients showed a higher $AVDO_2$ than patients without a reduced CBF, only in 3 out of 164 determinations on 55 patients they found an $AVDO_2$ exceeding 9 ml O_2/100ml, indicating real ischemia. In the other cases CBF was reduced in relation to a reduction in $CMRO_2$. The frequency of ischemia in this study is very low, but first CBF studies were in general performed within 96 hours after injury, and no conclusion can be drawn towards the occurrence of early ischemia after head injury.
Bouma et al focussed their attention on the early phase after trauma [53,73] and found in 31.4-33% of the cases studied within 6-8 hours after trauma, ischemic CBF values in combination with high $AVDO_2$ values.(table 6) In the total patient group, CBF values below 18 ml/100g/min were found in 13% of cases. CBF increased to normal or supra normal values during the first 24 hours after trauma and did not change at any time later in the posttraumatic course. The initial low CBF values correlated with outcome, suggesting that early ischemic events play a major role in the final outcome in patients with a severe head injury. CBF was related to the initial findings on CT scanning. Patients with a diffuse injury on the initial CT scan showed lower CBF values compared to patients with a focal injury. In patients with a focal injury, the ipsilateral side to the injury had a substantial lower CBF compared to the contralateral, non-injured side. Severe CBF reduction in and

around focal lesions was found by several other authors.[74,75] A similar CBF time course after severe head injury was found in other studies using 133Xe-CBF or TCD techniques.[56, 57,60,76,77,78]

Table 6. Cerebral blood flow and arterio-venous oxygen differences in head-injured patients measured at six-hour intervals postinjury

Hours post Injury	CBF	$AVDO_2$	% with ischemia
< 6	22.5 ± 5.2*	7.1 ± 1.5†	33
6-12	29.0 ± 10.0	6.3 ± 2.5†	11
12-18	33.3 ± 11.0	4.7 ± 1.6	0
18-24	34.8 ± 11.4	4.7 ± 1.6	5
24-30	33.9 ± 10.4	4.4 ± 2.4	3
30-36	33.2 ± 12.0	4.6 ± 1.4	4
36-42	36.9 ± 12.7	4.2 ± 1.7	5
42-48	34.8 ± 14.7	3.9 ± 1.1	0
> 48	33.6 ± 12.2	4.4 ± 1.6	5

CBF = Cerebral blood Flow (ml/100g/min), $AVDO_2$ = arterio-venous difference of oxygen content (ml/100ml/min). Ischemia is defined as CBF ≤ 18 ml/100g/min.
* Significantly lower than values in all later time intervals.
† significantly higher than values in later time intervals.
Adapted from Bouma et al.[53]

1.4 Why brain tissue PO_2 monitoring?

At the start of the studies of the underlying thesis there were no other clinically applicable monitoring techniques than those mentioned in section 1.3.2., that could provide continuous information on CBF or oxygen status of the brain. The need for a simple and technically reliable monitor that provides direct information on the oxygen status of the brain was recognized. The development of micro sensor technology for continuous measurements of partial oxygen pressure in tissue provided opportunities to measure the local brain tissue partial pressure ($P_{br}O_2$). Following initial testing in animal experiments [79,80,81] we developed this technique for clinical application.

1. 4.1 Technique of measuring brain tissue PO_2 [82]

In the underlying studies brain tissue PO_2 is measured with an electrode according to the Clark principle. A very small electrode with a diameter of 0.5 mm contains a closed polarographic cell with reversible electro-chemical electrodes. Oxygen diffuses trough the polyethylene wall of the electrode, into the electrolyte chamber. In this electrolyte chamber, O_2 is transformed to OH^- at the gold kathode. The reduction of O_2 provides the raw signal of the electrode (figure 3).
$2H2O + O_2 \leftrightarrow 2H2O_2 \leftrightarrow 4OH^- + 4e$

The electrode averages the brain tissue PO_2 near the tip of the catheter in a cylindrical tissue layer. The effective sample area of the used catheter is 14 mm^2. The technique is influenced by temperature with a change of catheter readings of approximately 4% per degree Celsius. Every catheter is checked by the manufacturer for its specific temperature sensitivity and this value is provided for every individual catheter. In combination with a micro temperature probe, continuously measuring brain tissue temperature, automatic correction for temperature changes can be programmed into the display readings. If no brain tissue temperature probe is available the central body temperature should be used to correct the device. In the ICU the rectal temperature is used for correction of the temperature sensitivity in most cases. At body temperature the T90 of the micro catheter is 60 seconds, which means that 90% of the actual PO_2 is measured within 60 seconds.

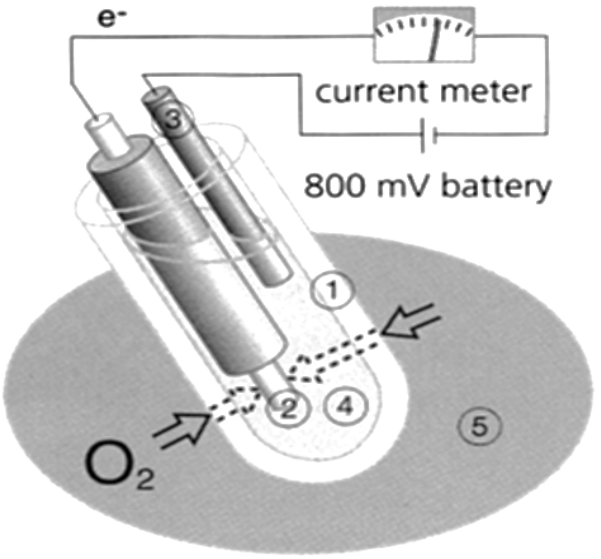

Figure 3. Function of the microelectrode. O_2 diffuses from the tissue (5) through the polyethylene membrane (1) into the electrolyte chamber (4). At the cathode O_2 is transformed and produces a current that is representative for the amount of O_2. 3 is the anode. Because the reversibility of the reactions the electrode remains stable over a longer period. Adapted from: GMS, Licox brochure: Rev 03_E / 05_99.

During the manufacturing process every individual catheter is calibrated for multiple parameters as: PO_2 sensitivity, temperature coefficient of the PO_2 sensitivity, and the zero current (electrode signal at a PO_2 level of 0 mmHg). All these parameters are provided by the manufacturer, in the early stage of the studies these values had to be installed on the device, and in a later period automatic installation by a smartcard was performed. During the monitoring period recalibration is not possible without violating basic sterile prescriptions. After ending the monitoring period, zero display error and PO_2 sensitivity drift can be

checked. In the early stage of the studies zero display error proved to be 1.2 ± 0.8 mmHg and PO_2 sensitivity drift at open-air level < 10%, with a mean monitoring time of approximately 100 hours.

Insertion technique.

In the clinical setting the micro electrode is inserted into the frontal lobe of the brain. Preferably the right side is chosen, unless a large contusion was visible on the admission CT scan or a skull fracture or skin lacerations made insertion impossible, the left frontal lobe was chosen.
After making a little burr hole (Ø 6mm) with a twist drill, the dura mater is punctured. Afterwards a modified intra cranial bolt is applied into the twist drill hole. The selftapping bolt has three channels; one for the PO_2 micro electrode, one for the ICP sensor and one for an optional catheter (e.g. Laser Doppler, temperature sensor or microdialysis tube). The manufacturer provides an insertion tool for the micro electrode, that ensures that every electrode is inserted at the same depth in the same way. The O_2 sensitive area is 29 to 35 mm below the brain surface in the white matter.(figure 4)

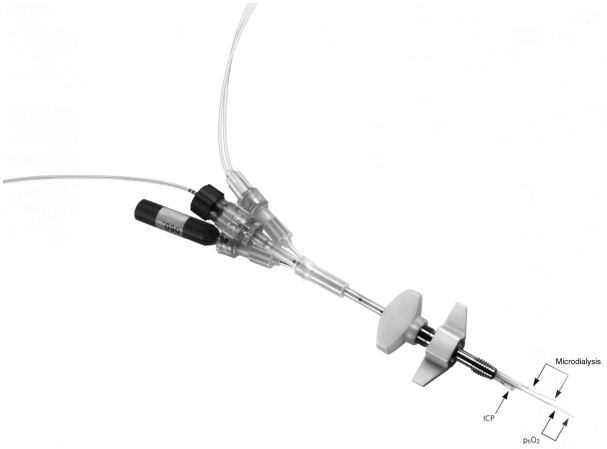

Figure 4: Specially developed intracranial bolt, with three channels. A special insertion tool is provided to ensure that the O_2 sensitive area is in between 29 and 35 mm below the brain surface.(LICOX, GMS, Kiel, Germany)

Introduction of the micro catheter unavoidably results in microtrauma of the brain tissue. In normal conditions this region of traumatized tissue is negligible.[81] However, immediately after insertion of the catheter the PO_2 reading is still influenced by this traumatized area. Initial recordings therefore do not provide valid information. Clinical practice showed a run-in time of 30-120 minutes. In the underlying studies data from this initial period were excluded from analysis.
In conclusion: the value provided by the micro electrode represents the amount of dissolved O_2 in the interstitial fluid and corresponds to the amount of oxygen that is available at the cellular level. Hence, it displays the balance between oxygen offer and demand. An increase in the PO_2 value can be due to an increase in oxygen offer or a decrease in demand.

Short-term variations in brain tissue PO_2 level may result from variations in diameter of the regulating vessels. The tissue oxygen value is most significantly determined by the mean distance between the functionally perfused capillaries per tissue volume. More longstanding variations in the tissue oxygen value can be due to changes in $CMRO_2$ (demand) or oxygen availability (vascular side).

1.5 Aims of the studies

After the micro PO_2 electrode proved to be stable and reliable in animal experiments and first experiences in patients showed to be valuable [79,80], the underlying studies were started. Aims of the studies were:

1. Is the PO_2 micro catheter save and reliable in a clinical setting?(chapter 2,3)
2. A. What is the normal brain tissue PO_2 value ($P_{br}O_2$)? (chapter 2,3)
   B. By which parameter(s) is the $P_{br}O_2$ value influenced? (chapter 2,3)
3. What is the time course of the $P_{br}O_2$ value after a severe head injury? (chapter 2,3)
4. Are the initial low $P_{br}O_2$ values real or an artifact? (chapter 2,3)
5. Is there any relation between low $P_{br}O_2$ values and clinical parameters, as outcome? (chapter 2,3)
6. What is the influence of arterial PCO_2 on $P_{br}O_2$? And is this influence of clinical importance?(chapter 5)
7. What is the influence of arterial PO_2 on $P_{br}O_2$? And is this influence of clinical importance? (chapter 4)
8. Is the local $P_{br}O_2$ value representative for the global brain oxygenation? (chapter 6)
9. Does a relationship exist between $P_{br}O_2$ values and Transcranial Doppler values? (chapter 7)

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CHAPTER 2

Continuous Monitoring of Brain Tissue PO_2 in Severe Head Injury

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Neurosurgery Vol. 38(1), january 1996, 21-31.

Abstract

Ischemia is one of the major factors causing secondary brain damage after severe head injury. We have investigated the value of continuous partial pressure of brain tissue oxygen ($P_{br}O_2$) monitoring as a parameter for cerebral oxygenation in 22 patients with severe head injury (GCS ≤ 8). Jugular bulb oxygenation, intracranial pressure and cerebral perfusion pressure were simultaneously recorded. O_2 and CO_2 reactivity tests were performed daily to evaluate oxygen autoregulatory mechanisms. $P_{br}O_2$ monitoring was started an average of 7.0 hrs after trauma with a mean duration of 74.3 hrs. No complications were seen, and the calibration of the catheters after measurement showed a zero drift of 1.2 ± 0.8 mmHg and a sensitivity drift of 9.7 ± 5.3%.

In 86% of the patients $P_{br}O_2$ was < 20 mmHg in the acute phase. Mean $P_{br}O_2$ significantly increased during the first 24 hours after injury. Two distinct patterns of change of $P_{br}O_2$ over time were noted. The first pattern was characterized by normal stable levels after 24 hours, and the second was characterized by transiently elevated levels of $P_{br}O_2$ during the second and third days. $P_{br}O_2$ values ≤ 5 mmHg within 24 hours after trauma negatively correlated with outcome. O_2 reactivity was significantly lower in patients with a good outcomes. CO_2 reactivity showed no constant pattern of change over time and was not correlated with outcome. Increased hyperventilation was shown to decrease $P_{br}O_2$ in some patients. Accurate detection of the moment of cerebral death was possible on the basis of $P_{br}O_2$ measurements. The correlation between $P_{br}O_2$ and other parameters such as ICP and CPP was weak. We conclude that $P_{br}O_2$ monitoring is a safe and clinically applicable method in patients with severe head injury. The early occurrence of ischemia after head injury can be monitored on a continuous basis. Deficiency of oxygen autoregulatory mechanisms can be demonstrated, and their occurrence is inversely related to outcome. For practical clinical use, the method seemed superior to jugular oxymetry.

Key words: Brain Tissue PO_2, Head Injury, Jugular Oxymetry, Outcome.

2.1 Introduction

After severe head injury various mechanisms lead to secondary brain damage, resulting in increased mortality and morbidity. The final common pathway of these mechanisms is cerebral ischemia. Recent studies have emphasized the importance of maintaining adequate cerebral perfusion pressure (CPP) in patients with head injury[1,2]. There is a need for techniques to continuously monitor cerebral oxygenation. Measurements of jugular bulb oxygenation (SjO_2) are becoming increasingly important. SjO_2 levels < 50% are considered as critical, below which ischaemia is a potential risk [3,4,5]. High SjO_2 values are supposed to represent hyperemia. However, two major problems exist in continuous SjO_2 monitoring with jugular catheters: first of all the technique is susceptible to technical artefacts. Low light intensity, movement artefacts and changes in catheter position are causes of unreliable recordings, sometimes in as much as 50% of the recording time. Second, even in the presence of normal or high SjO_2 values cerebral oxygenation can be impeded. Vasodilation can result in shunting of blood through short capillaries being ineffective in transport of oxygen to the brain tissue. Moreover, when flow is absent in one of the segments of the arterial vessels there is no oxygen transfer in the involved cerebral tissue and hence, the absolute regional ischemia will not be reflected by changes in oxygen saturation in the venous blood.
In experimental studies we have shown the feasibility of continuous monitoring of brain tissue pO_2 and further hypothesized on the presence of an oxygen autoregulatory mechanism in the brain [6,7]. Preliminary clinical studies showed promising results [7,8]. In these studies $P_{br}O_2$ was of predictive value for outcome after severe head injury, and seemed to be a measure for global cerebral ischemia. In this paper we report on further clinical experience in monitoring brain tissue PO_2 in patients with severe head injury, as a parameter for cerebral oxygenation. The aim of this study was to verify whether continuous $P_{br}O_2$ monitoring is applicable in patients with severe head injury and to gain more experience and insight in the value of this new parameter.

2.2 Material and methods

Patient population and treatment protocol

22 patients (17 male and five female) with a severe head injury were investigated. The mean age was 26 years (range 11-52). Informed consent for participation in the study was obtained from the nearest of kin. All patients had a Glasgow Coma Score (GCS) scores of ≤ 8 after resuscitation or deteriorated to this level within 8 hours after trauma. The mean GCS was 6.2 ± 1.4. After stabilization, an admission CT-scan was performed. Mass lesions were evacuated when indicated (seven patients). All patients were admitted to the neurosurgical intensive care unit and treated according to a standard protocol. This included intubation, artificial ventilation, monitoring of arterial blood pressure (ABP), heart rate, pulse oxymetry (SaO_2),

intracranial pressure (ICP), cerebral perfusion pressure (CPP=mABP - ICP), jugular bulb oxymetry (SjO_2) and end-tidal PCO_2. These data were stored at 1-hour intervals. Arterial blood samples were regularly taken for blood gas analysis. The patients were sedated and paralyzed. ICP was intraparenchymally monitored with a fiberoptic device (Camino^R). SjO_2 was monitored with a 4 French flexible near-infrared catheter (Oximetrix^R, Abbot). The catheter values were recalibrated every 12 hours on the basis of co-oximeter determinations of SjO_2. Increased ICP was treated according to a staircase model, when values > 25 mmHg were recorded for at least 5 minutes, patients were moderately hyperventilated to a P_aCO_2 of 30.0 mmHg. If ICP remained higher than 25 mmHg, despite hyperventilation, mannitol infusions were instituted at intervals of 3 to 4 hours. When these measures were insufficient to control ICP, barbiturates were administered (two patients).

Brain tissue PO_2 monitoring

$P_{br}O_2$ was monitored with a polarographic micro catheter (Clark type) with a diameter of 0.5 mm and a 5 mm long PO_2 sensitive area connected to a Licox^R PO_2 device (GMS, Kiel, Germany). The response time (T90) at 37°C was approximately 80 seconds. $P_{br}O_2$ values were stored at 15-seconds intervals. For introducing the ICP and $P_{br}O_2$ catheters, a special intracranial bolt with three entries was used. In all patients the intracranial bolt was placed at the right frontal region. Before insertion of the PO_2 catheter, catheter-specific calibration values specified by the manufacturer, were instituted on the PO_2 device. Corrections for variations in central body temperature were made. $P_{br}O_2$ recordings lasted for 5 days after trauma, or ended when ICP monitoring was no longer indicated. At the end of the observation period, the PO_2 microcatheters were calibrated for zero value and sensitivity drift. For zero-value calibration, a sterile fluid that was fully saturated with N_2 was used. This fluid has an actual PO_2 of zero. The PO_2 microcatheter was immersed in this fluid until stable values were obtained. The difference from zero was called the postmeasurement zero drift. Sensitivity drift calibration was performed by suspending the catheter in room air until stable values were obtained. Room air PO_2 is approximately 20% of the actual air pressure. At room air pressure of 760 mmHg, PO_2 should be 154 mmHg. The difference between the measured value and the calculated value, given the baromatic pressure, was called the sensitivity drift. Both callibration procedures each required 30 minutes.

O_2 and CO_2 reactivity

O_2 reactivity was calculated by determining the response of $P_{br}O_2$ to changes in P_aO_2 effectuated by increasing the inspired oxygen content (FiO_2). CO_2 reactivity was determined by observing the response of $P_{br}O_2$ to changes in P_aCO_2. Baseline values were observed during a 30-minute period, before inducement of changes in ventilator settings, and blood gases were analyzed as reference values. After changing the ventilator settings, a period of 10 minutes was observed to obtain stable values, and at the end of this period, all parameters were noted and blood

gases analyzed again. Before starting the procedure, patients were sedated and paralyzed, and during the procedure, no other drugs were administered.

For testing O_2 reactivity the FiO_2 was increased in steps of 20% untill 100%was reached, inducing an increase of P_aO_2.
O_2 reactivity was calculated as percentage change in $P_{br}O_2$ divided by the actual change in P_aO_2:

$$O_2\ \text{reactivity} = \frac{P_{br}O_{2(100\%)} - P_{br}O_{2(start)}}{P_{br}O_{2(start)}} \times \frac{1}{P_aO_{2(100\%)} - P_aO_{2(start)}} \times 100$$

$P_{br}O_{2(100\%)}$, $P_aO_{2(100\%)}$= $P_{br}O_2$ value respective P_aO_2 at a FiO_2 of 100%
$P_{br}O_{2(start)}$, $P_aO_{2(start)}$= $P_{br}O_2$ value respective P_aO_2 at the beginning of the O_2 reactivity test(baseline value).

Changes in P_aCO_2 were induced by increasing the inspiratory minute volume (IMV) by 20%, and subsequently decreasing the IMV to 10% less than the initial values. If during the changes in IMV, ICP increased > 25 mmHg when it was initially below this level, the tests were prematurely ended and the ventilator immediately reset (one patient).
CO_2 reactivity was calculated as percentage change in $P_{br}O_2$ divided by the actual change in P_aCO_2:

$$CO_2\ \text{reactivity} = \frac{P_{br}O_{2(+20\%)} - P_{br}O_{2(start)}}{P_{br}O_{2(start)}} \times \frac{1}{P_aCO_{2(+20\%)} - P_aCO_{2(start)}} \times 100$$

$P_{br}O_{2(100\%)}$, $P_aCO_{2(100\%)}$= $P_{br}O_2$ value respective P_aCO_2 with a FiO_2 of 100%
$P_{br}O_{2(start)}$, $P_aCO_{2(start)}$= $P_{br}O_2$ value respective P_aCO_2 at the beginning of the CO_2 reactivity test(baseline value).

2.3 Results

Monitoring of $P_{br}O_2$ started an average 7.0 hours after trauma (range 3.5-23 hours). The mean duration of monitoring was 74.3 hours (range 4.0-113.5 hours). In 18 patients, monitoring started within 10 hours after trauma, in 4 patients it started beyond this period. In one patient, this was because of technical problems, in the other three the initiation of the monitoring was delayed, because of emergency operations. In 11 patients the measurements were terminated before day 5 after trauma; 5 patients died, in 5 patients ICP levels remained low, not indicating further ICP-monitoring; in 1 patient the O_2 catheter broke at day 4 after trauma. No catheter-related complications were observed, in particular, no infections or catheter-related hematomas were seen.

The O_2 microcatheter was calibrated after termination of measurements in 14 patients. Mean zero drift was 1.2 ± 0.8 mmHg (range 0.1-3.4 mmHg) and mean sensitivity drift at open air level was 9.7 ± 5.3% (range 0.6-18.7%) at a mean recording time of 86.1 hours (range 15.4-113.5 hours).

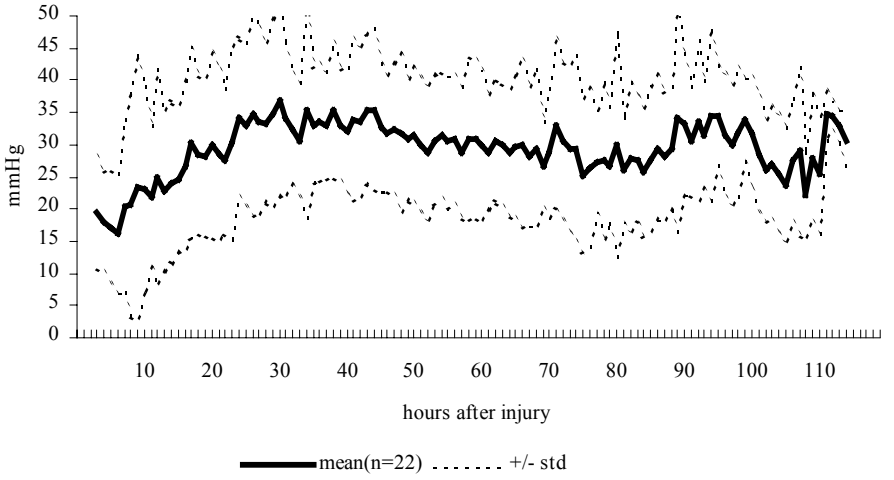

Figure 1. Time course of mean $P_{br}O_2$ values (± std) in 22 patients. During the first 24 hours after trauma a significant rise in mean $P_{br}O_2$ can be seen (P=0.002; Mann Whitney test).

Brain tissue PO_2 measurements

In all patients, stable recordings were obtained and no obvious technical artefacts could be seen to influence the measurements. The time course of $P_{br}O_2$ values averaged over all patients is shown in fig. 1. In 19 of the 22 patients, initially low values of $P_{br}O_2$ ($P_{br}O_2 \leq 20$ mmHg) were observed. A significant increase in mean

Table 1. Relation between $P_{br}O_2$ within 24 hours after trauma and outcome.

	6 months outcome		
$P_{br}O_2$	dead/PVS	alive	total
≤ 5 mmHg	4	1	5
> 5 mmHg	1	15	16
Total	5	16	21

The difference in outcome between the two groups is significant at the P=0.04 level, Fischer Exact test.

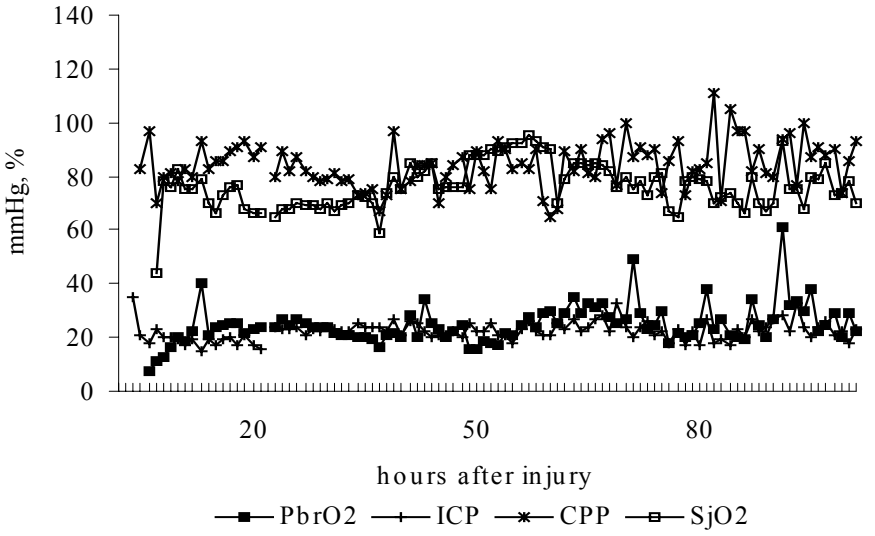

Figure 2[a]. One hour interval recording of a patient with initial low $P_{br}O_2$ values increasing to levels around 30 mmHg within 24 hours after injury. ICP, CPP and SjO_2 values are also given at an one hour interval .

$P_{br}O_2$ values during the first 24 hours after trauma was observed (P=0.002; Wilcoxon test), increasing from 16.6 ± 9.1 mmHg to relatively high levels of 35.8 ± 14.7 mmHg. During the second day after trauma, a decline of the mean $P_{br}O_2$ to mean values of 25.1 ± 12.2 mmHg was noted.

Because, theoretically, the observed time course of mean $P_{br}O_2$ could be influenced by changing numbers of patients, because some died early or recovered, the same analysis was performed for patients monitored over 96 hours. Also, in this analysis, the same pattern of changes in mean $P_{br}O_2$ over time was noted.

In individual patients two distinct patterns of changes in $P_{br}O_2$ over time were seen:

1. Initially low values increased to levels of approximately 30 mmHg on average within 24 hours after injury (range 20-36 hrs), and then stabilized at this level. This pattern was seen in 10 patients (fig. 2a).
2. Initially low values increased to levels higher than normal from 12 to 48 hours after trauma, and returned to normal or slightly elevated levels within 36 to 72 hours. This pattern of response, characterized by temporarily elevated levels of $P_{br}O_2$, was seen in 9 patients (fig 2b).

The other three patients did not fit into one of these two patterns:
two patients died early, and 1 patient showed stable values from the onset of measurements.

In 4 patients, waveforms could be observed in the $P_{br}O_2$ recordings. These wave forms did not show a consistent pattern and differed among patients in frequency, amplitude and duration. Waveforms were only present during relatively short

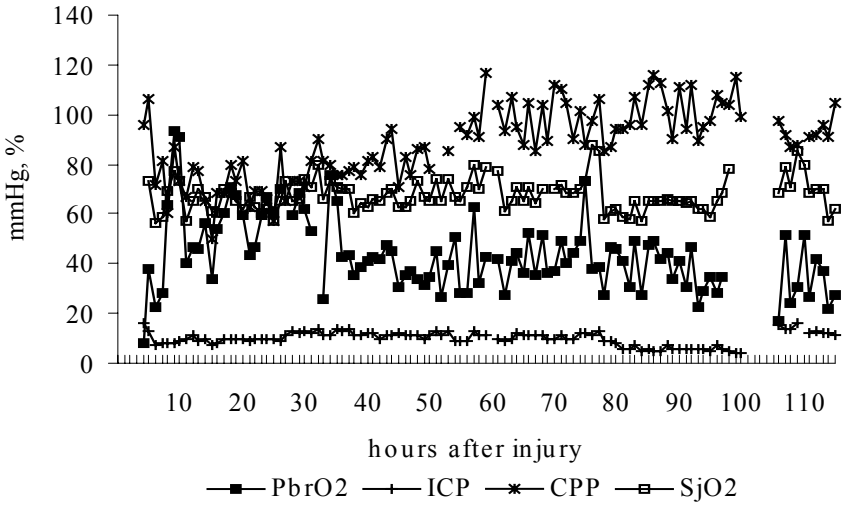

Figure 2[b]. One hour interval recording of a patient with initial low $P_{br}O_2$ values increasing to levels above normal within 10 hours after injury, returning to normal $P_{br}O_2$ levels 36 hours after injury. ICP, CPP and SjO_2 values are also given at an one hour interval.

periods of the recording time, varying between 12 and 32 hours with an amplitude of 7 to 25 mmHg. An example of waves occurring on the $P_{br}O_2$ recordings is shown in fig. 3. There was no relationship between the observed waves and either CPP, ICP or SjO_2.

Six out of the 22 patients had $P_{br}O_2$ values of ≤ 5 mmHg. The mean duration per patient for these low values was 4.3 hours (0.5-7.1 hrs). In 5 of these 6 patients, low values were measured within the first 24 hours after trauma. The early low $P_{br}O_2$ values of ≤ 5 mmHg correlated negatively with outcome 6 months after trauma (table 1). Four of the 5 patients with very low $P_{br}O_2$ values within 24 hours after trauma died. The difference in outcome between the patients with and without $P_{br}O_2$ values of ≤ 5 mmHg was significant at a level of $P<0.04$ level (Fischer's Exact Test). In 1 patient with low $P_{br}O_2$ values within 24 hours after trauma who survived, the CT scan showed a right frontal contusion.

$P_{br}O_2$ values of ≤ 5 mmHg within 24 hours after trauma were not correlated to the post resuscitation Glasgow Coma Scale score, age, sex, or presence of hypoxia before resuscitation (table 2).

$P_{br}O_2$ values of ≤ 5 mmHg after the initial post-traumatic period occurred in 3 patients. In 2 patients this happened at the moment of cerebral herniation and brain death. This is demonstrated in fig. 4. In the other patient, several relatively short periods of low $P_{br}O_2$ values were seen immediately after tracheal suctioning

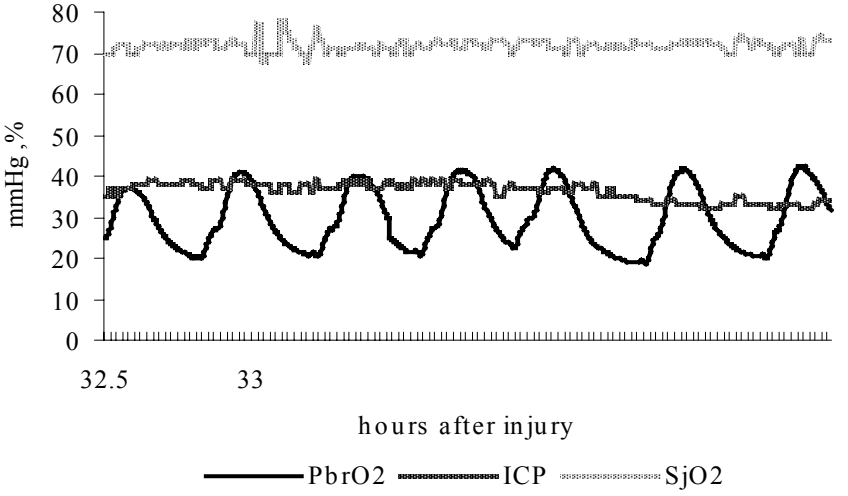

Figure 3. $P_{br}O_2$ recordings demonstrating a clear waveform pattern in one patient. There is no correlation with ICP or as SjO_2 recordings.

procedures when the ICP increased and CPP temporarily decreased. In this patient, there also was a cerebral contusion in the right frontal lobe. The low values in this patient probably are indicative of regional ischemia and not of global ischemia.

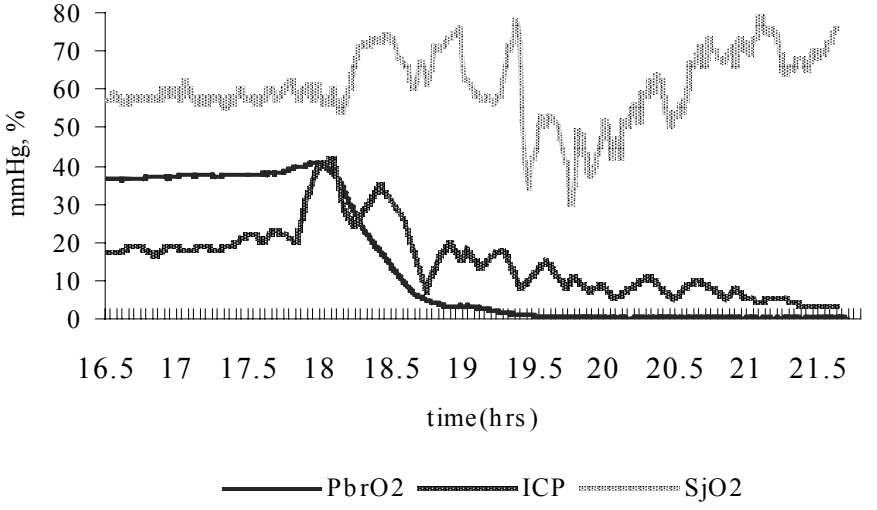

Figure 4. Typical $P_{br}O_2$ recording during cerebral herniation and occurrence of brain death.

Table 2. Characteristics of the five patients with initial low $P_{br}O_2$ values compared with the other patients.

				post resucsitation values						CT-scan	
pat number	age	sex	GCS	mABP	mICP	mCPP	$mSjO_2$	P_aO_2	P_aCO_2	shift	SAH
1	16	F	5	84	8	76	60	77.4	28.5	4	yes
6	17	M	7	104	20	84	unkn.	262.9	36.0	5	yes
13	29	M	7	128	21	107	73	100.6	41.3	11	no
18	31	M	5	89	40	49	39	170.5	30.8	15	yes
20	11	M	3	75	33	42	80	unkn.	unkn.	0	yes
mean 5	20.8		5.4	96.0	24.4	71.6	63.0	153.2	34.5	7.0	
Std 5	8.7		1.7	20.8	12.4	26.5	18.0	83.4	6.0	6.0	
mean others	28.1		6.4	101.4	21.2	83.8	65.2	162.2	30.8	3.0	
Std others	10.2		1.2	27.2	11.7	13.7	14.2	44.3	6.0	4.7	
P-value	0.26		0.18	0.24	0.43	0.26	0.95	0.21	0.56	0.09	

Initial characteristic values are given for the 5 patients with initial $P_{br}O_2 \leq 5$ mmHg. Mean ± standard deviation of the initial characteristic values are listed for the 5 patients with initial low $P_{br}O_2$ values (mean 5, Std 5) and the patients without initial low $P_{br}O_2$ values (mean others, Std others). No statistical difference (P-value) of the mean characteristic values are found between these two groups of patients (Mann-Whitney test). M = male; F = female; mABP, mICP, mCPP, P_aO_2, P_aCO_2 are given in mmHg; SjO_2 in %; SAH = subarachnoid hemorrhage; unkn. = unknown; shift = maximal shift of midline structures in mm.

Factors influencing $P_{br}O_2$

The records of individual patients were scrutinized to detect factors influencing $P_{br}O_2$. The major influence was exerted by changes in P_aO_2 and to a lesser extent by changes in P_aCO_2 and the extent of sedation and paralysis. The effects of P_aO_2 on $P_{br}O_2$ were noted most during preoxygenation prior to tracheal suctioning procedures. However, the response in individual patients was variable; in general patients showed a large increase in $P_{br}O_2$ (fig. 5). In some patients the depth of sedation and paralysis seemed to influence $P_{br}O_2$, lower values being noted at deeper sedation. No effect of mannitol infusions could be seen on $P_{br}O_2$.

To analyze the relationship between $P_{br}O_2$ and mABP, ICP and CPP the 1-hour values were analyzed. Although in individual patients some effects of changes in mABP, ICP or CPP could be seen on $P_{br}O_2$, this response was variable and, over the total population, the correlation was absent, as demonstrated by low correlation coefficients of .096 to 0.19 for these parameters.

O_2 reactivity tests were performed in 18 out of 22 patients studied. A linear relation between $P_{br}O_2$ and P_aO_2 over the ranges measured was found with a mean correlation coefficient in individual patients of .93 ± .13. Differences in O_2 reactivity were found during the period of observation within a patient and among

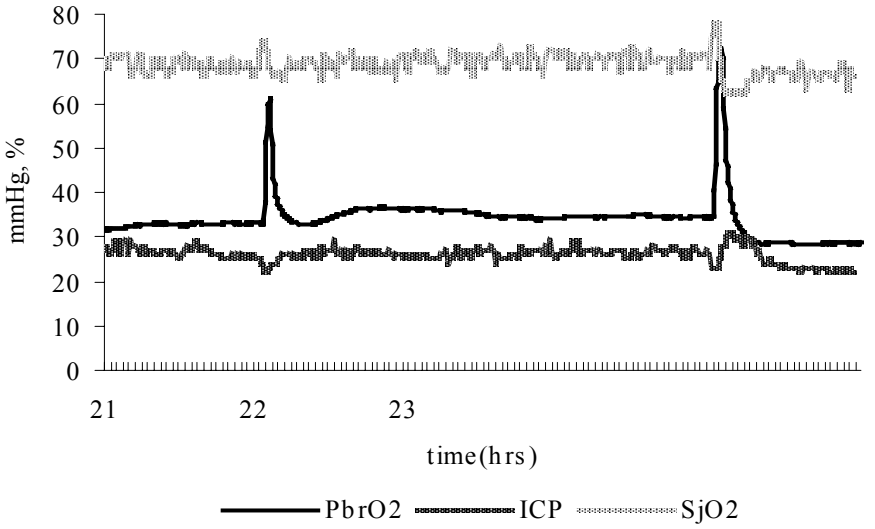

Figure 5. $PbrO_2$ during tracheal suctioning procedures. During preoxygenation prior to tracheal suctioning a sharp increase in $P_{br}O_2$ can be observed. Simultaneously a minor decrease in ICP and increase in SjO_2 values can be seen. (TS = start preoxygenation prior to tracheal suctioning procedure).

patients (fig. 6). For the total period of observation, a significant difference in mean O_2 reactivity was found between patients with favorable and unfavorable outcome (P=0.0003; Mann Whitney test). Patients with good outcomes had lower O_2 reactivity than did patients with poor outcomes. When the data were analyzed per day, a significant difference in O_2 reactivity could also be found between these two groups on day 1 (P=0.02; Mann Whitney). During the subsequent days no statistical difference was seen.

For the total group of patients mean O_2 reactivity on day 1 was 4.03 ± 3.10 $mmHg^{-1}$. Compared with the other days of observation, this was the lowest mean value, but differences did not reach statistical significance. In the patients with a favorable outcomes mean O_2 reactivity showed a significant increase during the period of observation (P=0.02; student's T-test). In patients with an unfavorable outcomes O_2 reactivity remained high (table 3).

The O_2 reactivity was separately analyzed between the two groups of patients, demonstrating the different patterns of $P_{br}O_2$ change over time, as described. In the second group, characterized by temporary elevation of $P_{br}O_2$, the mean O_2 reactivity was significantly higher (P=0.02 Mann Whitney test). No correlation could be demonstrated between O_2 reactivity and postresuscitation GCS, ICP or CPP.

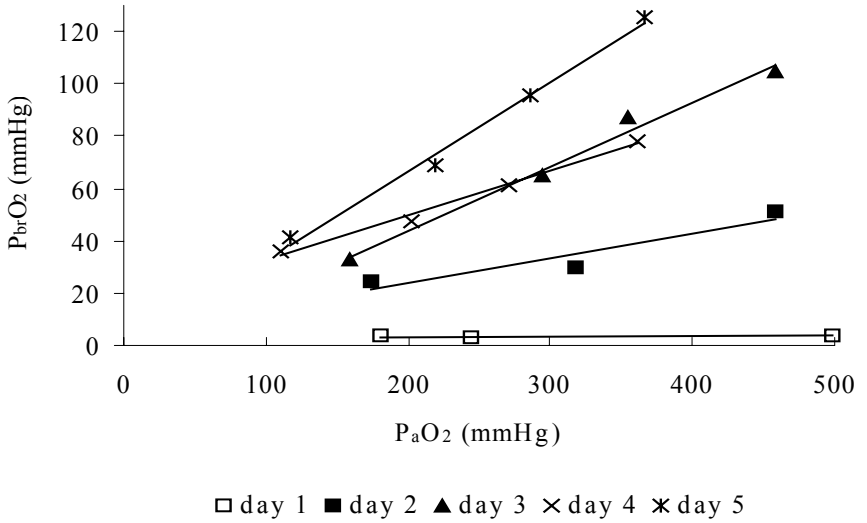

Figure 6. Linear regression lines between $P_{br}O_2$ and P_aO_2 in a single patient during O_2 reactivity tests, differentiated for every day after trauma. A clear positive relationship exists between $P_{br}O_2$ and P_aO_2.

CO_2 reactivity

Eighteen patients underwent CO_2 reactivity tests. In 1 patient, studies on day 4 were prematurely ended because ICP increased to > 25 mmHg at a slight rise in P_aCO_2. The correlation between $P_{br}O_2$ and P_aCO_2 in all patients was weak and varied among patients and in patients during periods of observations. A mean correlation coefficient of 0.32 ± 0.26 was found. To compute CO_2 reactivity, baseline values

Table 3. Relation between O_2 reactivity ($mmHg^{-1}$) ± std and outcome, 6 months after injury, at different time periods after injury.

		O2 REACTIVITY		
Observation period	all patients (N)	GOS 1,2,3 (N)	GOS 4,5 (N)	P value Mann Whitney
all days	5.50±3.61 (67)	7.07±3.59 (31)	4.14±3.06 (36)	.0003
day 1	4.03±3.10 (14)	6.23±3.29 (6)	2.38±1.70 (8)	.0201
day 2	5.72±4.42 (16)	7.80±5.20 (7)	4.09±3.08 (9)	.0640
day 3	6.20±2.67 (15)	7.37±2.59 (7)	5.18±2.43 (8)	NS
day 4	5.98±3.88 (13)	6.94±2.96 (6)	5.15±4.59 (7)	NS
day 5	5.51±3.86 (9)	6.81±4.37 (5)	3.88±2.81 (4)	NS

Significant difference in O_2 reactivity between patients with favourable and unfavourable outcome most pronounced on day 1; in patients with a favourable outcome there is also a significant difference in O_2 reactivity between day 1 and day 3 (P=0.02, student T-test). NS = not statistically significant.

Table 4. Relation between CO_2 reactivity ($mmHg^{-1}$) ± std and outcome, 6 months after injury, at different time periods after injury.

	CO2 REACTIVITY			
Observation period	total group (N)	GOS 1,2,3 (N)	GOS 4,5 (N)	P value Mann Whitney
all days	1.98±5.90 (67)	2.75±5.13 (30)	1.35±6.46 (37)	NS
day 1	-1.11±4.15 (14)	-.40±3.42 (6)	-1.64±4.78 (8)	NS
day 2	1.41±3.98 (15)	2.46±4.84 (6)	.71±3.43 (9)	NS
day 3	3.88±7.56 (15)	1.95±2.47 (7)	5.57±10.11 (8)	NS
day 4	1.42±5.91 (13)	4.77±5.04 (6)	-1.45±5.28 (7)	NS
day 5	5.01±6.17 (10)	5.56±8.59 (5)	4.46±3.35 (5)	NS

No significant difference was seen between CO_2 reactivity and outcome group; on day 1 CO_2 reactivity was significantly lower than on day 3 and 5 (P=0.04, resp. 0.02, student T-test). NS = not statistically significantly different.± 14% and mean post-calibration values 66 ± 10%. These values did not differ significantly. In 81% of the calibrations the SjO_2 value had to be readjusted, with a range of -29% / 31% and in 25% of all calibrations readjustment of the SjO_2 value was over 10%.

and values after increasing the IMV by 20% were used. The induced changes in P_aCO_2 however, were small, varying between 3.8 mmHg on day 1 and 2.3 mmHg

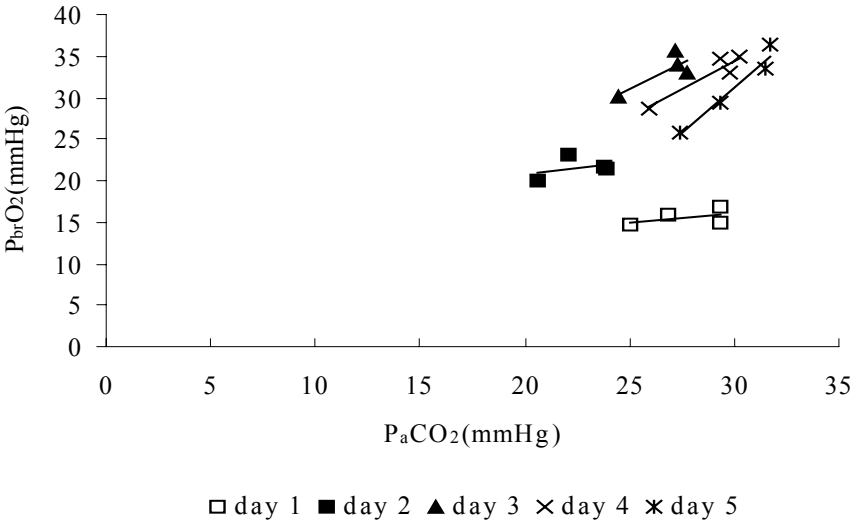

Figure 7. Linear regression lines between $P_{br}O_2$ and arterial PCO_2 (P_aCO_2) in a single patient during CO_2 reactivity tests, differentiated for every day after trauma. In this patient a clear positive relationship exists between $P_{br}O_2$ and P_aCO_2, which is most prominent during day 5 after trauma (R=.97; P=.03). ICP levels are on day 1 between 18 and 25 mmHg, on day 2 between 12 and 15 mmHg, on day 3 between 17 and 28 mmHg, on day 4 between 26 and 30 mmHg and on day 5 between 20 and 26 mmHg.

on days 2 and 3. On all days, a decrease in mean $P_{br}O_2$ was found after a period of hyperventilation, most prominent on day 5 after injury (fig. 7).
The mean CO_2 reactivity on day 1 was significantly lower than that on day 3 ($P < 0.04$) and 5 ($P < 0.02$; student T-test)(table 4).
In contrast to the data on O_2 reactivity, no relationship existed between CO_2 reactivity and outcome. Nor was there any relation between CO_2 reactivity and post resuscitation GCS, ICP and CPP.

$P_{br}O_2$ and SjO_2

Jugular bulb oxymetry was performed in 17 out of 22 patients and started on average 7.5 hours (range 2.5-12) after trauma. The mean recording time was 97.0 hours (range 15.8 - 144). Every 12 hours, the catheter was calibrated in vivo. In 13.6 ± 12.7% of the total recording time, and in 17.7 ± 17.6% during the first 24 hours after trauma, the obtained values were unreliable because of technical problems. In 16 patients, 95 calibrations were performed. Mean precalibration values were 67 ± 14%, and the mean postcalibration values were 66 ± 10%. These values did not significantly differ. In 81 % of the calibrations, the SjO_2 value had to be readjusted, with a range of –29 to 31 %, and in 25% of all calibrations, readjustment of the SjO_2 value was > 10%.
Mean SjO_2 time course showed a pattern similar to the mean $P_{br}O_2$ time course. During the first 24 hours after trauma, mean SjO_2 values were approximately 65% and increased utill mean values of nearly 80% 60 hours after trauma (fig. 8).

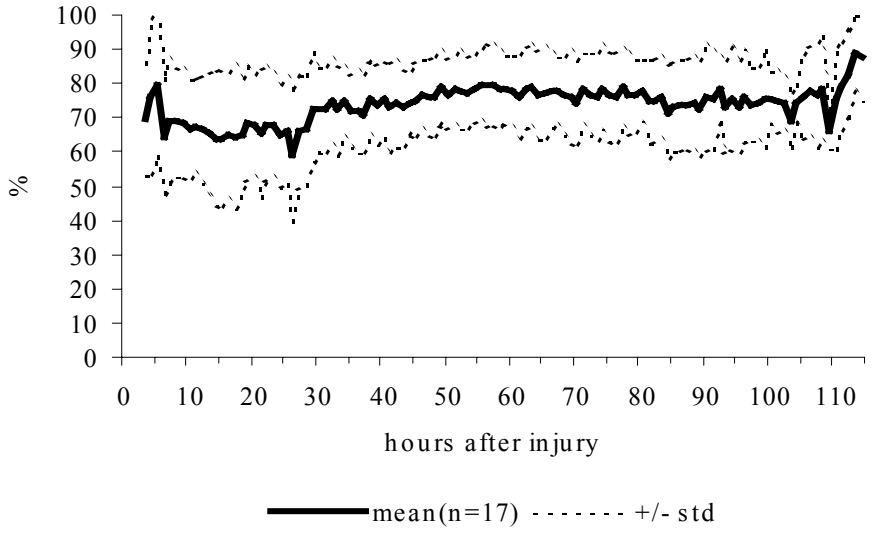

Figure 8. Time course of mean SjO_2 values ± std after trauma.

Mean correlation between $P_{br}O_2$ and SjO_2 was 0.35 ± 0.25 (range -0.13 /0.72). In only 2 patients was a correlation of > 0.7 found. Low $P_{br}O_2$ levels were not always accompanied by low SjO_2 levels, on the contrary, in some patients high SjO_2 values were seen when $P_{br}O_2$ was low (fig. 9a and 9b).

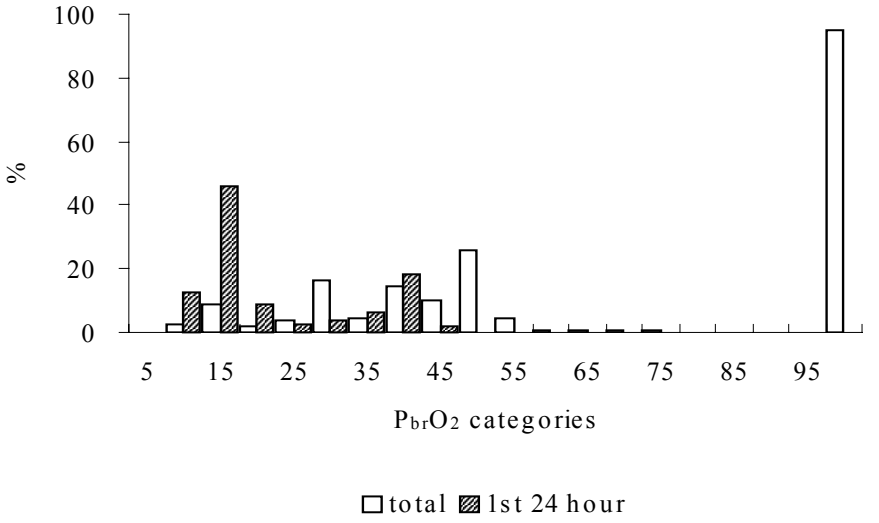

Figure 9[a]: Frequency histogram of $P_{br}O_2$ values given for the first 24 hours after trauma and for the whole period of observation. $P_{br}O_2$ values are categorized in groups with an interval of 5 mmHg. A clear difference in the percentage of low values can be seen between the first 24 hours and the total observation period.

2.4 Discussion

In this study, $P_{br}O_2$ measurements have proven to be a clinically applicable, easy-to-handle and reliable monitoring technique. Only once were measurements prematurely ended because the catheter connection to the intracranial bolt broke. No infections at the catheter site were seen. During several days of measurements, the $P_{br}O_2$ microcatheters proved to be accurate and did not show serious drift, so there was no need for comprehansive calibration procedures. Preinsertion calibration is possible, with calibration of the catheter in an O_2 free nitrogen solution and subsequently in room air. This procedure, however, takes about 1 hour and has the potential risk of compromising sterility. Therefore, we chose to use the manufacturer's catheter-specific calibration settings. The postmeasurement re-calibration results have validated this approach. We think that the technique of $P_{br}O_2$ monitoring is superior to continuous jugular bulb oxymetry regarding the stability of the recordings. In jugular bulb oxymetry, in vivo calibrations are required every 12 hours. Sheinberg et al. [9] have demonstrated a very good

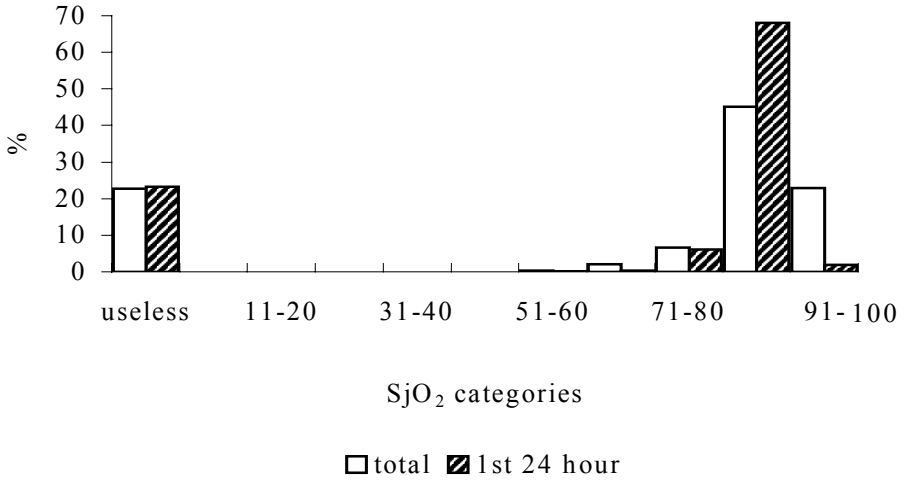

Figure 9[b]: Frequency histogram of the same patient as in figure 9[a] of SjO_2 values given for the first 24 hours after trauma and for the whole observation period. During the first 24 hours after trauma, high SjO_2 values can be observed. In this time period, $P_{br}O_2$ values were low. Note the high number (± 22%) of unreliable SjO_2 values, caused by technical artifacts, such as low light intensity levels.

correlation between SjO_2 values obtained by catheter and those by direct measurement of O_2 saturation by a co-oximeter. In our studies we also found an excellent correlation between pre- and postcallibration values of SjO_2, but readjustments of > 10% were made in 25% of the calibrations performed. The number and degree of readjustments performed in the jugular oxymetry calibrations are undesirable in a monitoring technique for routine clinical use.

Few data exist on normal values of brain tissue PO_2 in humans. In the experimental situation, we found normal values of $P_{br}O_2$ of 25-30 mmHg at an P_aO_2 of 102-104 mmHg in dogs [7]. These values agree with the measurements obtained in patients under stable conditions. Values of 33-36 mmHg have been reported by Assad et al. [10] in three patients at a P_aO_2 of 150-170 mmHg. These values, however, were measured during brain tumor surgery, and therefore, whether these can be considered representative of a normal situation is debatable. Higher values of $P_{br}O_2$ have been reported by Kayama et al.[11] and Meixensberger et al.[12]. Their measurements, however, were performed with surface electrodes, and in the study of Kayama et al. the measurements were performed in peritumoral edematous tissue. It is conceivable that with surface electrodes the presence of outside air can influence the measurements, causing falsely high levels of $P_{br}O_2$ values. Alternatively, it is conceivable that in surface measurements, the PO_2 in subarachnoid CSF is measured. In the experimental situation, we found PO_2 levels of 41 to 47 mmHg in the subarachnoid CSF [7].

We have no explanation for the occurrence of wave forms as observed in 4 patients. In the case demonstrated in fig. 3 the $P_{br}O_2$ levels at the top of the waves reach levels known to exist in subarachnoid CSF. Control CT scan studies in this patient

demonstrated the catheter to lie deeply in the frontal lobe approaching the midline. Whether the waves demonstrated in this patient result from intermittent contact with the subarachnoid CSF or represent a true physiologic phenomenon remains unresolved.

The observed results of the $P_{br}O_2$ measurements should be critically appraised, as should those of any new monitoring technique. In the majority of patients studied, initially low $P_{br}O_2$ values were observed. The question can be raised whether these low levels are real or the result of catheter related artifacts. Directly after positioning the PO_2 electrode, generally high values were seen decreasing to the described low levels within 10 to 20 minutes. This can obviously be considered to be an artefact caused by manipulation of the catheter on introduction and subsequent temperature equilibration. A period of at least 30 to 45 minutes of equilibration is required before obtaining valid data. Hence, the data analysis in this study was only performed on recordings after this period. The slow increase over many hours in $P_{br}O_2$ observed in the majority of patients did not have the characteristics of an artifact, and such a response was not seen in the animal experiments performed earlier, either [6]. It is, therefore, our considered opinion that the initially low $P_{br}O_2$ values seen in patients for periods up to 24 hours after trauma present a real physiologic phenomenon and are indicative of cerebral ischemia in this early post-traumatic phase. This opinion is consistent with the results of several experimental studies investigating metabolic products with magnetic resonance imaging spectroscopy of a failing energy metabolism after head injury. Parallel to the severity of the induced trauma, the adenosine triphosphate content of the brain decreases and the content of inorganic phosphate increases, consistent with the presence of cerebral ischemia.[13,14,15]

Ischemic periods after head injury are common [16] and their occurrence and duration are negatively correlated with outcome. Accurate detection of these ischemic insults is difficult with the tcurrently available monitoring systems or requires comprehensive investigational methods.[9,17,18,19,20] During transcranial doppler studies, we demonstrated a “low flow velocity state” in 43% of the patients during the first 36 hours after trauma.[21] Fourty procent of the patients with low flow velocities died. Bouma et al. [22,23] showed with Xenon CT scanning in the very early phase after trauma that there is an ischemic episode in as many as 33% of the patients with severe head injury. In the studies presently described, 5 out of the 22 patients (23%) had $P_{br}O_2$ values of < 5 mmHg within 24 hours after trauma. Low $P_{br}O_2$ values within 24 hours after trauma suggest, therefore, a cerebral blood flow less than ischemic levels. Jaggi et al. [24] have demonstrated significantly depressed $CMRO_2$ levels in patients with severe head injury who died or remained vegetative. In our studies, we found very low levels of $P_{br}O_2 \leq 5$ mmHg, in the initial phase after trauma to indicate a poor prognosis. Four out of 5 patients with such low levels died. In the one surviving patient with a $P_{br}O_2$ of ≤ 5 mmHg, a cerebral contusion was present in the right frontal lobe, probably indicating local ischemia. It must be realized that a disadvantage of the technique used is that only very regional PO_2 is measured. Changes of $P_{br}O_2$ may occur in other regions of the brain not monitored. The catheter should preferably be placed in a relatively undamaged part of cerebral tissue, and the results measured can then be considered

indicative of global cerebral oxygenation. Given this presumption, it can be inferred from our studies that $P_{br}O_2$ levels of ≤ 5 mmHg are absolutely critical. In older studies, Jöbsis [25] calculated an upper limit PO_2 level of 5 mmHg as critical for acites tumor cells and liver cells, and Davies and Bronk [26] calculated that the cerebral cortex should function normally until the limiting level of < 5 mmHg PO_2 is reached. We would, however, not advocate a $P_{br}O_2$ level of 5 mmHg as a minimal requirement in patients with severe brain injury. The $P_{br}O_2$ levels in these patients, prone to secondary brain damage, should preferably be maintained at higher levels, probably between 10 and 15 mmHg. The level of $P_{br}O_2$ below which ischemia can be considered a hazard in these patients, however, has yet to be more accurately detirmined.

A $P_{br}O_2$ of ≤ 5 mmHg beyond the initial 24 hours after trauma occurred in only 3 patients. In 2 of these patients, this occurred during the development of brain death and cessation of cerebral circulation. It is remarkable as demonstrated in fig. 4 that at the moment of herniation and subsequent brain death, a sharp decrease of $P_{br}O_2$ to levels just higher than zero is seen, without being preceded by intermittent low levels or a gradual decline in $P_{br}O_2$. As also shown in figure 4, SjO_2 increases at the cessation of circulation. We think that the actual moment of occurrence of brain death can be accurately determined on basis of the $P_{br}O_2$ measurements. The diagnosis of brain death itself, however, cannot be made on the basis of the $P_{br}O_2$ measurements alone because of the regional character of the measurements. However, given the clinical diagnosis of brain death, the moment at which cessation of cerebral circulation occurs can be determined and the further investigations, legally required before transplant procedures, can than be instituted without delay. On the basis of SjO_2 levels, the moment that brain death occurs cannot be accurately determined because high SjO_2 levels can also be caused by luxury perfusion or shunting. Besides, when cerebral circulation ceases, blood flow in the jugular vein will be diminished and, consequently, SjO_2 values can become inaccurate because of low light intensity levels. In the one patient in whom short episodes of low $P_{br}O_2$ values were observed after 24 hours after trauma, there was also a right frontal lobe contusion. Again, in this patient the low levels could be considered indicative of local ischemia.

$P_{br}O_2$ is thought to reflect the balance between oxygen offer and demand. Oxygen offer is determined by arterial oxygen content and CBF; the demand is determined by cerebral metabolism, inclusive of mitochondrial function. Decreased $P_{br}O_2$ can theoretically be caused by inadequate oxygen offer (i.e. low CBF) or increased metabolism. Increased $P_{br}O_2$ levels can result from uncoupling between CBF and metabolism or failure of an oxygen autoregulatory mechanism. Based on the results of our experimental studies we found evidence on the presence of an oxygen autoregulatory mechanism. Recently, Meixensberger et al. also found evidence in clinical studies for such an oxygen autoregulatory response [12], although several authors in earlier years already hypothesized on the existence of an oxygen autoregulatory meachanism [27].

Evaluating the time course of $P_{br}O_2$ changes after trauma, we noted two patterns of response. In the first group, $P_{br}O_2$ increases after intially being low to stable levels between 24 and 48 hours after trauma. In the second group a period of elevated

levels was found after 36 to 72 hours. Indeed, in this second group a significantly higher O_2 reactivity was demonstrated, which we consider to be indicative of a disturbed autoregulatory response. High O_2 reactivity during the acute phase after trauma was also shown to correlate with a poor outcome. Disturbed O_2 regulatory mechanisms would therefore imply a more serious damage to the brain. In patients with a good outcomes, these mechanisms seem to be relatively spared in the initial phase. However, during subsequent days, an increase in O_2 reactivity is seen in all patients. During the last day of the studies (day 5), O_2 reactivity in patients with a good outcomes tended to decrease. Therefore, it can be inferred that disturbances in O_2 regulatory mechanisms are most pronounced during days 2 to 4.

$P_{br}O_2$-CO_2 reactivity did not show a constant pattern during the period of observation and was not related to outcome. The response in individual patients was variable. Theoretically $P_{br}O_2$ was expected to decrease when P_aCO_2 decreased, as vasoconstriction is known to reduce CBF. Such a response was indeed demonstrated in some patients as illustrated in fig. 7. However, the relationship was not this clear in every patient. A clear relation between P_aCO_2 and CBF and TCD recordings has been shown [28,29,30]. Possibly, the changes in P_aCO_2 effected during our studies were, in some patients, too small to elicit obvious responses. The variable response in CO_2 reactivity observed between patients can, however, be interpreted in a different way, namely, that on the basis of the CO_2 reactivity, the ability of the patients to tolerate more intensive hyperventilation therapy can be analyzed.

At the onset of the studies, we had hoped to find a clear correlation between the results of $P_{br}O_2$ measurements and the results of jugular oxymetry. Although a very good correlation existed in some patients, this was certainly not the case in all patients. In some patients in the early posttraumatic phase, we observed low levels of $P_{br}O_2$ when jugular oxygen saturation was high. Based on the jugular saturation, these patients would be considered hyperemic. These patients may have been hyperemic, but the blood was then probably shunted and ineffective in oxygen transport, resulting in ischemia at the tissue level. High SjO_2 values were also seen in patients with brain death, because of an absence of oxygen extraction by the cerebral tissue. Also, $P_{br}O_2$ was very low in these patients, near zero. We think, therefore, that a high jugular oxygen saturation does not preclude the presence of cerebral ischemia.

In our studies, we found no clear correlation between $P_{br}O_2$ and ICP or CPP. It may, therefore, be concluded that measurements of $P_{br}O_2$ in patients with severe head injury afford other valuable information and should be advocated in conjunction with ICP and CPP monitoring in these patients. The method is easily applicable in the clinical situation and, in our experience, is superior to jugular oxymetry, with regarding technical artifacts influencing the measurements. In our experience, better insight in cerebral oxygenation is obtained with $P_{br}O_2$ measurements. Further research is necessary to analyze whether therapy aimed at increasing $P_{br}O_2$ will yield better treatment results.

Acknowledgements

The authors wish to express their gratitude to Dr. A. Marmarou for valuable suggestions and comments during the studies, to Dr. C. Robertson for reviewing the manuscript, to Dr. W. Fleckenstein for his support during the studies and to Mrs. Nanda Elink Schuurman for typing the manuscript.

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CHAPTER 3

Brain Oxygen Tension in Severe Head Injury

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Neurosurgery 46(4): 868-878,2000

Abstract

Objective: Ensuring adequate cerebral oxygenation and perfusion is of fundamental importance in the treatment of patients with acute cerebral disorders. Online continuous monitoring of brain oxygenation is possible with a parenchymal microelectrode that measures local brain oxygen tension ($P_{br}O2$). The ultimate question is whether therapeutic approaches can be targeted based on such monitoring. Before this question can be addressed, the technique requires validation in the clinical setting. The frequency of occurrence of low values, and its relation to outcome need to be established.

*Methods:*One hundred one comatose head-injured patients (Glasgow Coma Scale score ≤ 8) were studied. $P_{br}O2$ probes were inserted in an undamaged part of the frontal region. Patients were treated in conformance with the European Brain Injury Consortium guidelines. Outcome at six months was determined by Glasgow Outcome Scale score.

*Results:*Early brain tissue hypoxia was frequently observed, despite aggressive treatment for intracranial pressure and cerebral perfusion pressure. Values lower than 15 mmHg, for a duration longer than 30 minutes, were observed in 57 patients. Values lower than 10 mm Hg in 42 patients, and lower than 5 mm Hg in 22 patients, were observed during the first 24 hours. Depth and duration of tissue hypoxia were related to outcome and proved to be an independent predictor of unfavorable outcome and death.

*Conclusion:*Monitoring the partial oxygen pressure of local brain tissue is a safe and reliable method to monitor cerebral oxygenation. Because brain tissue hypoxia occurs frequently, and is significantly related to poor outcome, future efforts should be aimed at the treatment of brain tissue hypoxia. The effects of such “brain hypoxia-targeted” treatment need to be established in a multicenter study.

Key words:Brain oxygenation, Brain tissue oxygen partial pressure, Head injury, Multitechnique monitoring, Prognosis.

3.1 Introduction

Cerebral ischemia is common after severe head injury. Ischemic changes have been observed in more than 90% of patients dying from head injury.[1,2] Bouma et al. reported the occurrence of low cerebral blood flow (CBF) in the ultraearly post-traumatic period.[3] Cerebral ischemia results from intrinsic pathophysiological pathways and from systemic insults, such as hypotension and hypoxia. Such systemic insults are frequent in the early post-traumatic period [4] as well as in the intensive care setting.[5] The adverse influence of systemic insults on outcome has been well documented.[6,7,8] Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) therapy are currently the main therapeutic pillars in the treatment of severe head injury.[9,10] The aim is to ensure that CBF and oxygenation, are adequate to meet metabolic demands. Multitechnique monitoring and preliminary results of microdialysis in severe head injury have increased our understanding of metabolism and oxygenation. The focus of multitechnique monitoring in head injury is primarily on CBF and oxygenation. Our group has previously reported on the feasibility, safety, and initial experience of continuous monitoring of local partial oxygen pressure of brain tissue ($P_{br}O_2$).[11] In that report on a study of 22 patients with severe head injury we documented the presence of early ischemia at the tissue level. Questions were raised, however, as to whether the observed initial low $P_{br}O_2$ values actually reflected oxygen pressure at the tissue level or were possibly caused by a technical catheter related phenomenon. Thus, we extended our series to 101 patients, who underwent evaluation with the GOS after six months. The present report focuses on the occurrence, depth, and duration of initial low values, and their relation to clinical and computed tomographic (CT) characteristics and patient outcome.

3.2 Patients and Methods

Patient characteristics and treatment protocols

Data from multitechnique monitoring, including $P_{br}O_2$were collected prospectively in a series of 101 patients with severe nonpenetrating head injury (GCS < 8) who were admitted to the neurosurgical intensive care unit of the Academic Hospital Rotterdam from September 1992 until November 1997. In all patients an early CT-scan was obtained at admission or from the referring hospital. Routinely a second CT-scan was acquired within 24 hours, or earlier if indicated. The initial CT-scans were coded according to the Trauma Coma Data Bank (TCDB)-protocol.[12] The ventricles were scored as asymmetrical or symmetrical; the status of the cisterns was scored in three grades: as normal, compressed, or absent, and the presence of intraventricular blood was noted. The extent of midline shift was evaluated in three categories: 0-5 mm, 5-10 mm and more than 10 mm. The presence, location and extent of subarachnoid blood were noted, and scores were given for the presence of intracranial lesions according to their space occupying effect and their nature.

Finally, the intracranial diagnosis was graded according to the six-point-scale published by Marshall et al. .[12] All patients received standard intensive care treatment and monitoring, conforming to the principles of recently published European Brain Injury Consortium (EBIC)-guidelines.[13] Outcome was evaluated at 3 and 6 months after trauma, according to the GOS.[14] For purposes of analysis the GOS was dichotomized into unfavorable (Dead, Vegetative State, Severely Disabled) and favorable (Moderately Disabled, Good Recovery) outcomes.

Monitoring, data acquisition, and analysis

Heart rate, respiratory rate, mean arterial blood pressure, peripheral oxygen saturation, ICP and CPP as well as $P_{br}O_2$ were monitored in all patients. Mean arterial blood pressure was monitored with a pressure transducer calibrated at the level of the heart. Intracranial transducers were inserted into the brain parenchyma through a modified three channel intracranial bolt with an outer diameter of 6 mm. Unless a cranial fracture, hemorrhage, or contusion was present the bolt was inserted at the right frontal side. ICP was monitored using the Camino fiberoptic device (Camino, San Diego, CA, USA). $P_{br}O_2$ was monitored using a Clark type microcatheter and a Licox $PbrO_2$ measuring computer (Licox, GMS, Kiel Mielkendorf, Germany). In six patients, a second $P_{br}O_2$ catheter was introduced through the third channel in the bolt. All physiologically monitored data were acquired with a custom designed software package (CDAI, University Hospital Rotterdam, Rotterdam, The Netherlands), stored using a Novell network onto a 3 gigabyte hard disk. All files were scrutinized for contamination and for artifacts related to nursing care, or patient transport by one experienced research nurse (W.J.). At 24 hour intervals, the reactivity of the cerebral oxygenation to 100% oxygen and hyperventilation was tested. These episodes were eliminated from the data reported here, and will be reported elsewhere. When the measurements were concluded, the catheters were tested for zero drift (zero display error), using an absolute zero solution ($Na_2S_2O_4$) and for sensitivity drift at room air (PO_2 display error). Actual room air PO_2 was calculated from local barometric pressures, obtained from the meteorological institute and measured humidity (ambient PO_2 = 20.9% of dry barometric pressure).

Statistical analysis

Data are presented as means ± standard deviation. Statistical analysis was performed using the chi-square statistic when testing for associations of nominal data. The relationship between an unfavorable outcome and initial low $P_{br}O_2$ values was analyzed with a restricted cubic spline function [15], as implemented in S-plus software (Data-analysis Products, Division of Mass Soft, Inc., Seattle, WA, USA). For this analysis, time periods with $P_{br}O_2$ values lower than 5, 10 and 15 mm Hg respectively were labeled. If the cumulative period was longer than 30 minutes, these patients were considered to have had low initial $P_{br}O_2$ values. Correlations of clinical and CT-scan parameters with $P_{br}O_2$ values were expressed as Spearman rank correlation coefficients. The prognostic value of $P_{br}O_2$ measurements was determined by correlating outcome with the main clinical and CT-scan variables

using a multivariable logistical regression analysis (SPSS Software, SPSS Inc., Chicago, IL, USA). A P-value < 0.05 was considered statistically significant.

3.3 Results

Demographics and CT-scan characteristics

In total 101 patients were enrolled in the study. Eighty-three patients were men and 18 were women; the mean age was 34 years (range 11-82). Seventy-two patients had been involved in motor vehicle accidents. This distribution is typical in a population of patients with severe head injury. Detailed demographic and clinical data for the patients are displayed in table 1. CT characteristics are shown in table 2. The severity of injuries in the population studied is represented by the occurrence of pupillary abnormalities in 50% of the patients, partial or complete obliteration of basal cisterns in 61% and an overall mortality of 39%.

Table 1. Demographic data (n = 101)

	No. of patients
Sex	
Male	83
Female	18
Type of injury	
Motor vehicle accident	32
Other traffic accident	40
Fall	21
Other	8
Mean age (yr) (range)	34 ± 16 (11-82 years)
Glasgow Coma scale score	
3-8	42
6-8	59
Pupils	
both reactive	51
one non reactive	30
both non reactive	20
Outcome 6 at months	
Unfavorable	54
dead	39
persist. vegetative	1
severely disabled	14
Favorable	47
moderately disabled	17
good	30

Duration and reliability of $P_{br}O_2$ monitoring

$P_{br}O_2$ monitoring was started as soon as possible after injury (mean 7.0 ± 3.5 hours). The duration of $PbrO_2$ monitoring was intended to last 5 days; however, monitoring was terminated earlier if the patient died or if ICP monitoring was no longer considered indicated.

Eighty-three patients were monitored for more than 24 hours, in three patients who were monitored, post hoc analysis was not possible owing to computer related errors. The average duration of monitoring was 86 hours (range 4-180 hours).

Adverse events and complications related to catheter introduction and monitoring were not seen. Postmeasurement calibration resulted in an average zero display error of 0.42 ± 0.85 mmHg. PO_2 display error (sensitivity drift), calibrated at a mean room air PO_2 of 157.6 ± 1.5 mm Hg, was 0 ± 6%.

Table 2. CT-scan characteristics in 101 patients with a severe head injury

	No. of patients
Ventricular asymmetry	40
Basal cisterns	
present	40
compressed	35
absent	26
Intraventricular blood present	23
Midline shift	
0-5 mm	75
5-10 mm	14
≥ 10 mm	12
Subarachnoid blood	
none	52
cisterns	7
convexity	28
both cisterns and convexity	14
Intracranial diagnosis	
diffuse injury, no CT-pathology	10
diffuse injury, normal cisterns	24
diffuse injury with swelling	27
diffuse injury with shift	1
mass lesion surgically evacuated	24
epidural hematoma	9
acute subdural hematoma	15
mass lesion not surgically evacuated	15
acute subdural hematoma	1
intracerebral hematoma	3
contusion	11

Time course and pattern of $P_{br}O_2$

Mean $P_{br}O_2$ time course with standard deviations averaged over all patients is shown in figure 1. Low initial values were common in the first 12 to 24 hours after injury, occurring in over 50% of patients. A detailed analysis of the frequency of occurrence of such low values during the first 24 hours after injury was performed. Values lower than 15 mm Hg were observed in 57 cases, values lower than 10 mm Hg in 42 cases and values lower than 5 mm Hg were found in 22 cases. Patients with documented hypoxia on admission did not necessarily have lower values during the measurement period. In 30 of the patients with initial low values an overshoot phenomenon was observed with a mean high value of $P_{br}O_2$ of 46 mm Hg in the 36 to 48-hour period after injury. No relation between presence or absence of an overshoot phenomenon and documented hypoxia or hypotension at admission could be demonstrated, and the occurrence of overshoot was not related to outcome.

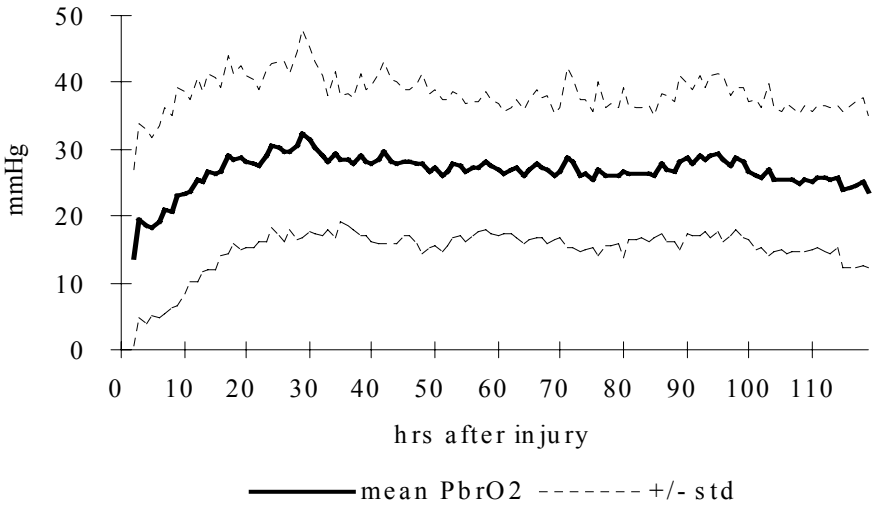

Figure 1. Average $P_{br}O_2$ measurements of 100 patients during the first 120 hours. Mean and standard deviations of values measured in hours after injury are displayed. Note the initial low values with a rapid increase during the first hours and a slower increase over the first day. Stabilization occurs at 25 to 30 mmHg.

Evaluation of run in time

In six patients comparative measurements of $P_{br}O_2$ were performed with two catheters introduced through the three-way bolt. The second catheter was introduced after a variable period of 4 to 24 hours. Absolute values of $P_{br}O_2$ between the two catheters differed considerably (table 3). After the introduction of the second catheter, lower values were seen initially, despite a stable $P_{br}O_2$ recording obtained from the first catheter. These initial low values quickly increased to stable values.

Table 3. Comparative measurements[a].

Patient No.	Catheter 1	Catheter 2
1	27	32
2	40	29
3	38	21
4	24	58
5	16	20
6	41	20

[a]Numbers show absolute values of PbrO2 in mmHg

The duration of this stabilization was variable, but in all cases it was within a 2-hour run-in period (figure 2). When both catheters displayed stable $P_{br}O_2$ values the absolute values were not necessarily equal, but fluctuations of both catheters were simultaneous and in the same direction.

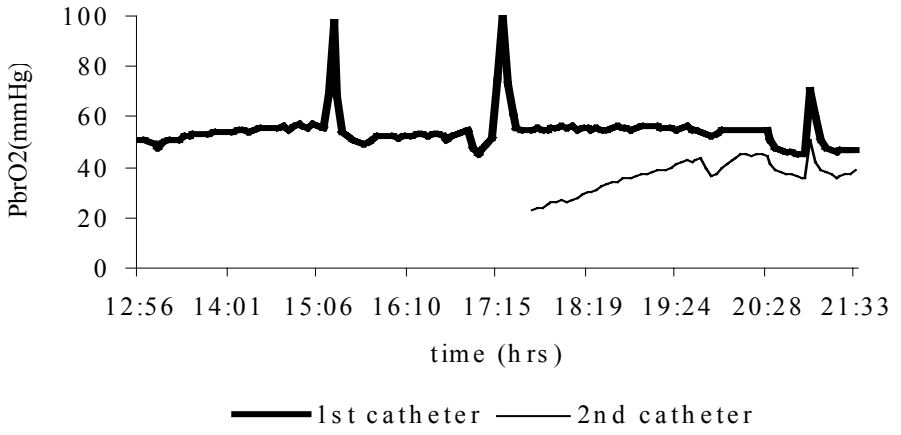

Figure 2. Example of comparative measurements of two catheters. During a stable period of the first catheter, a run-in time of two hours of the second catheter can be observed. Hereafter this second catheter is also stable, and the $P_{br}O_2$ fluctuations are similar in both time and relative height.

Relation of measured $P_{br}O_2$ values to clinical and CT scan characteristics

The association between the occurrence of low values in the first 24 hours after trauma and clinical variables, such as age, GCS, pupils, ICP and presence of multiple injuries, as well as CT characteristics, was analyzed with the Spearman rank coefficient. No significant correlations were found for clinical variables; of the CT characteristics the only parameter significantly correlating with initial low $P_{br}O_2$

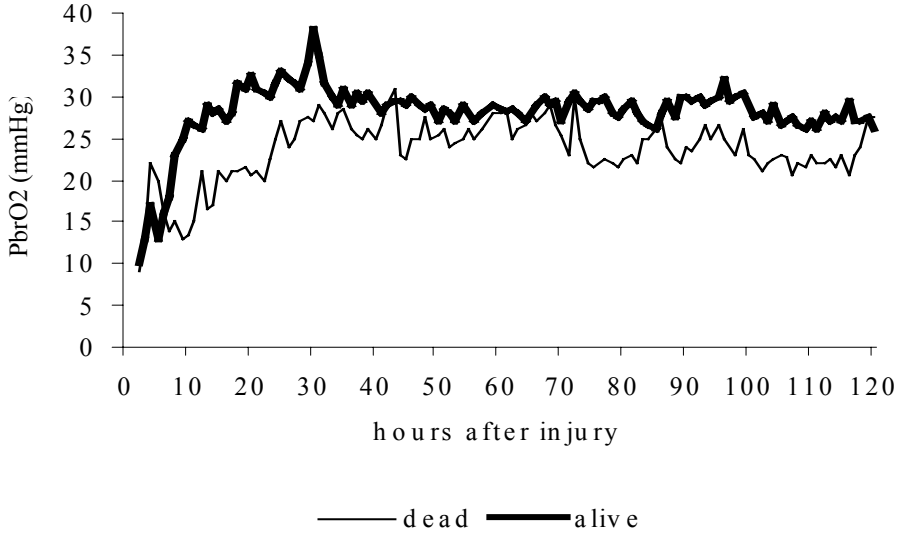

Figure 3. Mean $P_{br}O_2$ values in patients that were dead (thin line) or alive (thick line) after six months. The patients who died had a lower $P_{br}O_2$ during the entire monitoring period, most pronounced during the first 36 hours.

values was compression of the cisterns. For analysis of the relation between $P_{br}O_2$ and ICP, patients were dichotomized into two groups, according to ICP levels measured within the first 24 hour period: in the first group, ICP was consistently below 25 mmHg (n = 46); in the second group ICP was raised above 25 mm Hg for a period of 60 minutes or longer (n = 54). No correlation was found between patients with and without raised ICP and presence or absence of low $P_{br}O_2$ values. Results of the analysis are summarized in table 4.

Table 4. Spearman Rank Coefficient (r) Correlation between $P_{br}O_2$< 10 mm Hg for > 30 minutes with patient' characteristics

Patients' Characteristics	r	P-value
Clinical variables		
Age	.04	.69
GCS	-.08	.55
Pupil	.08	.46
multi trauma	-.06	.54
ICP	.09	.38
CT variables		
Shift	.13	.21
Cisterns	.34	.001
tSAH	.05	.64
CT classification	.13	.19

Prognostic value of $P_{br}O_2$ in relation to known prognostic variables

Higher $P_{br}O_2$ values were found during the entire measurement period in survivors (figure 3). The association between initial low values ($P_{br}O_2 \leq 10$ mmHg) with mortality or unfavorable outcome is shown in table 5. Twenty-four of 43 patients with low initial values died, as compared to 14 out of 66 patients without these low values. When patient outcome was dichotomized into unfavorable versus favorable a similar significant association was found. The odds ratio for death was 3.8 (P=0.002) and the odds ratio for an unfavorable outcome was 2.8 (P=0.015).

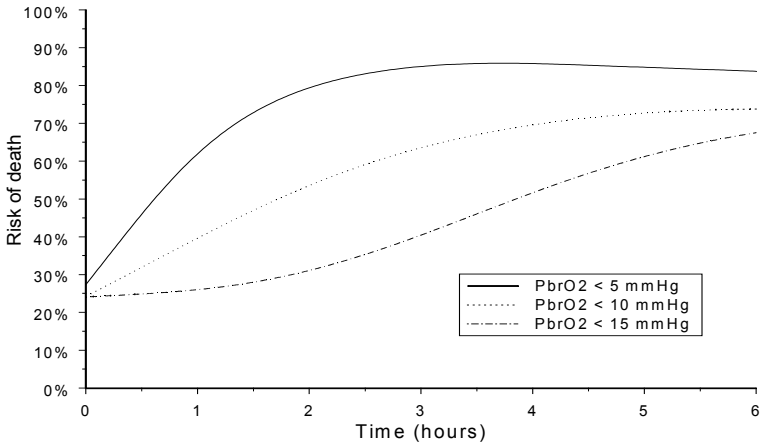

Figure 4. Restricted cubic spline functions of the relative risk of death, related to initial low values categorized into lower than 5, lower than 10 and lower than 15 mmHg. The ordinal characterization follows from the layering of the curves, lower than 5 being worse than lower than 10, being worse than lower than 15. Note that the curves stabilize at long durations of hypoxia.

For further analysis of the predictive significance of low $P_{br}O_2$ values, including adjustment for other predictive variables, low values within the first 24 hours were categorized into groups of < 5, < 10, and < 15 mmHg. Time periods during which low values were measured were summed. In figure 4 we observe that lower $P_{br}O_2$

Table 5. Relationship between duration of $P_{br}O_2$ < 10 mm Hg and Outcome at 6 months.

Duration (min)	alive	dead	Favorable Outcome	Unfavorable Outcome
< 30 min.	42	14	32	24
≥ 30 min.	19	24	14	29

values are related to higher risk of death. There is no exact threshold point in time after which the risk of death increases steeply. After several hours there is no increase in the risk of death indicating that the duration of low values below this period is indicative of impending death. During the first 1.5 hours several cutoff points of time were evaluated. The odds ratio for death was 3.8 (95% confidence interval, 1.6-8.9) at a duration of 30 minutes, and it was even more significant at durations of 45 and 60 minutes. Even a $P_{br}O_2$ value < 10 mm Hg for more than 10 minutes' duration carried a statistically significant risk of death.
We chose the cutoff point at a duration of 30 minutes or more for further analysis. In logistic regression models the low initial $P_{br}O_2$ remained an independent prognostic factor as $P_{br}O_2$ shown in table 6. Only the status of the peri-mesencephalic cisterns had a clearrelationship with and reduced the prognostic value. We note that the high odds ratio for $P_{br}O_2$ with adjustment for a combination of clinical and CT-scan variables in table 6 may reflect overfitting, as a relatively large number of variables was used, in comparison with the number of patients dying as a result of severe head injury.

Table 6. Multiple logistic regression analysis: Independent contribution of low $P_{br}O_2$ ($P_{br}O_2$ < 10 mmHg for > 30 minutes) adjusted for clinical and CT-scan parameters.

Variables	odds ratio for death (95% CI)	odds ratio for Unfavorable Outcome (95%CI)
low $P_{br}O_2$	3.8 (1.6-8.4)	2.8 (1.2-6.3)
adjusted for clinical variables:		
age	3.7 (1.6-8.9)	2.7 (1.2-6.3)
GCS	3.8 (1.6-9.0)	2.8 (1.2-6.6)
Pupils	4.0 (1.6-10)	3.0 (1.2-7.5)
multi trauma	3.7 (1.6-8.8)	2.9 (1.2-6.7)
ICP	4.1 (1.7-10)	3.0 (1.2-7.5)
adjusted for CT scan variables:		
CT classification	3.9 (1.6-9.7)	2.7 (1.1-6.4)
Cisterns	3.6 (1.3-9.4)	1.8 (0.7-4.5)
Shift	3.7 (1.5-9.0)	2.6 (1.1-6.1)
tSAH	4.3 (1.7-11)	3.0 (1.2-7.5)
adjusted for combination of variables:		
age + GCS + pupils	3.8 (1.4-9.9)	2.8 (1.0-7.4)
clinical + ICP + CT var.	6.0 (1.8-20)	5.3 (1.4-20)

3.4 Discussion

Reliability of $P_{br}O_2$ measurements

Intraparenchymal monitoring of $P_{br}O_2$ provides the clinician with additional information on the local oxygen status of the injured brain. Because no

complications such as hemorrhage or infection, are observed, the method is considered safe. The catheters show a negligible zero drift and a low sensitivity drift, confirming the technical reliability of the method in the clinical setting. The difference in absolute values of $P_{br}O_2$ measured in patients with two inserted probes reflects the heterogeneity of oxygenation at the tissue level.[16] These observations, although in a small study sample, emphasize the limitations of placing too much emphasis on absolute values of $P_{br}O_2$, and attempts to identify a critical threshold value of $P_{br}O_2$ should be viewed with caution. Local factors, such as the presence of micro hemorrhages around the oxygen probe may influence values measured.[17] That this may also occur in the clinical setting was observed in one of our patients in whom the oxygen probe was inadvertently placed in a small hemorrhagic contusion: despite low $P_{br}O_2$ recordings the patient made an excellent recovery. This observation illustrates the potential limitations of a local monitoring technique. We therefore recommend routine CT evaluation of the position of the oxygen sensor. If the investigator chooses to insert the oxygen probe in an undamaged area of the brain and local complicating factors are absent the recorded values can be considered representative of the other undamaged areas of brain tissue, taking the known heterogeneity of brain oxygenation into account. A local measure of oxygenation indicates changes in global oxygenation, as a global ischemic insult will reduce $P_{br}O_2$ in all areas of the brain. Values measured are dependent on the relation of the catheter to the capillary mesh, as they are influenced by both the diameter of the microvascular vessels and the diffusion distance between the capillary mesh and the oxygen probe.

Causes of tissue hypoxia and implications for monitoring techniques

Cerebral ischemia is generally considered to result from insufficient oxygen supply in relation to demand. With this concept in mind, monitoring of jugular venous saturation is considered appropriate for detecting global cerebral ischemia. Low jugular saturation values indicate a higher extraction of oxygen and thus are indicative of ischemia. However, the causes of tissue hypoxia are not easily explained. In an overview of the oxygen status of the blood, Siggaard-Andersen et al. [18] identified potential causes of tissue hypoxia. The main types of hypoxia, its causes, and the expected change in arterio-venous oxygen extraction are summarized in table 7. From this table it becomes evident that monitoring of venous oxygen saturation will not detect all causes of tissue hypoxia. Moreover, tissue hypoxia may be present despite normal or increased venous saturation values. We have previously reported that low $P_{br}O_2$ values were observed in the presence of normal or even high oxygen saturation values in the cerebral venous blood.[11] Local $P_{br}O_2$ can provide additional information on brain oxygenation, even when jugular bulb oximetry is already available. The results of the study by Kiening et al. [19] support this opinion.

Low initial $PbrO_2$

Real or artifact?

Clinical studies have shown critically reduced CBF following head injury.[3,8,20,21,22,23] Microdialysis has revealed the presence of lactic acidosis indicating ischemia at the tissue level.[24] In studies using transcranial Doppler sonography in patients with head injury we have observed low flow velocities in the early phase after trauma.[25] The observation of low brain tissue $P_{br}O_2$ in the first 24 hours after injury is consistent with these reports. However, comparative

Table 7. Causes of tissue hypoxia

Type of hypoxia	Cause	Expected change in $AVDO_2$
Ischemic hypoxia	Decrease in flow	Increase
Low extractivity hypoxia	Low arterial PO_2 (hypoxemic hypoxia)	
	Low Hb concentration (anemic hypoxia)	
	Low half saturation tension P50 (high affinity hypoxia)	No change
Shunt hypoxia	Arterio-venous shunting	Decrease
Dysperfusion hypoxia	Increased mean diffusion length from erythrocytes to mitochondria, caused by intracellular or interstitial edema	Decrease
Histotoxic hypoxia	Toxic agents	Decrease
Uncoupling hypoxia	Agents interfering with synthesis of ATP	
	Mitochondrial dysfunction	No change
Hypermetabolic hypoxia	Increased demand	Increase

P-50, oxygen half-saturation pressure of hemoglobin; ATP, adenosine 5'-triphosphate. According to Siggaard Andersen et al. . [12]

measurements indicate an artifactual low value during the first 2 hours of recordings. Some equilibration time is required before steady state measurements of the probe/tissue interface is can be attained; this time will probably depend on the type of catheter and the introducing method used. The catheters used in our studies have a small diameter (0.5 mm) and are very flexible. For insertion a stiff introducer (outer diameter 1.1 mm) is used, through which the catheter is passed into the brain tissue. The use of this introducer causes more extensive local tissue damage than would occur if the catheter itself was simply passed into the brain tissue and it is conceivable that this method disturbs microvascular flow surrounding the tip of the catheter. This hypothesis would explain the longer run in time observed in the clinical setting as compared with our experience in experimental situations, in which the microcatheters are introduced directly into the brain without the help of an introducer. In the laboratory setting a maximum equilibration time of 1 hour was found in animal experiments.[17]
Therefore the gradual increase of $P_{br}O_2$ over periods up to 12 to 24 hours, cannot be explained by the short run in time of 2 hours. We firmly believe that the observed

low values of $P_{br}O_2$ occurring after the run in time of 2 hours reflect the presence of local tissue hypoxia. This opinion is strengthened by the clear correlation between the presence of low values in the first 24 hours and poorer outcome. Whether the low $P_{br}O_2$ value early after injury reflects a change of CBF, or an increase in utilization, resulting in a decrease of oxygen concentration, can only be investigated by concurrent measurements of CBF and metabolism and this issue warrants further research.

Relationship among clinical parameters, CT-scan parameters and outcome

Clinical variables known to be associated with the outcome of head injured patients, such as age, GCS on admission, pupillary reactivity, ICP and presence of significant systemic trauma, are not significantly correlated with initial low values. Of CT-scan variables, known to have a prognostic value, only the status of the basal cisterns correlates with early tissue hypoxia. Because there is no straightforward correlation between clinical or CT-scan variables and the new monitoring technique, this technique might well provide additional utility, as shown by the multiple regression model. After a period of 10 minutes in which measured $P_{br}O2$ values were less than 10 mmHg, a significant correlation with death or unfavorable outcome was observed. The highest significance was reached after 60 minutes, but after 30 minutes the odds ratio for death was already 3.8. Adding the separate or combined clinical and CT-scan variables to the regression model did not cause a significant adjustment in the predictive value of low $P_{br}O_2$ values. Thus initial low $P_{br}O_2$ values are an independent predictor of death or unfavorable outcome.
Statistical analysis using a cubic spline function has the advantage of being very flexible while preserving the continuous character of a variable, resulting in smooth functional relationships. The relative risk of death for the three threshold values is graded (figure 4). In cases of deep local tissue hypoxia ($P_{br}O_2 < 5$ mmHg) a 50% risk of death occurs at about 30 minutes. For moderate hypoxia (< 10 mmHg) the same 50% risk of death occurs at 1 hour and 45 minutes, while for mild tissue hypoxia (< 15 mmHg) this point is reached in less than 4 hours. Jones et al. [26] , in an experimental setting, demonstrated the well-known effect of depth and duration of tissue hypoxia on neurological outcome. The present investigation of this novel monitoring technique confirms such a relationship in the traumatized human brain. Furthermore, this significant correlation of low $P_{br}O_2$ to poorer outcome supports our earlier conclusions that initial low values are not due to an artifact, but are evidence of a pathophysiological phenomenon frequently observed after head injury. Our data confirm our earlier finding on the relationship between low $P_{br}O_2$ and outcome.[27] Valadka et al. [28] studied 43 head-injured patients in whom different cutoff points were used in search of a clinical threshold. Using a Tobit regression analysis these authors concluded that both depth and duration of cerebral hypoxia have a relationship with mortality. The results of our analysis are in agreement with these findings and the restricted cubic spline analysis further emphasizes these important relationships.

Implications for therapy

We conclude that tissue oxygenation in patients with severe head injury can be reliably monitored on a continuous basis with the technique described, using an intra-parenchymally introduced Clark type PO_2 sensor. We have further shown that low values frequently occur in the first 24 hours after injury, and that the depth and duration of these low values are related to unfavorable outcome and death. Evidence therefore supports the concept of targeting therapy toward improvement of cerebral oxygenation. Such improvement can be obtained either by increasing the oxygen content of the arterial blood or by improving delivery through increase of flow. The latter method is the basis for CPP therapy. [10] In a recent study by Robertson et al. [29] no overall benefit with regard to outcome was seen in patients treated with a CBF targeted regime, which aimed to achieve a mean arterial pressure ≥ 90 mm Hg, as compared with patients treated with an ICP targeted regime. In this study however all patients were treated in accordance with one of the specified regimes, and CBF management was not specifically targeted to patients at risk for low CBF or cerebral hypoxia. $P_{br}O_2$ monitoring may help to identify those patients in whom CBF targeted therapy might be appropriate and what level of critical perfusion pressure is required in individual patients.

Correcting anemia and ensuring optimal saturation of the arterial blood is the most important method for improving oxygen content of the arterial blood. Increasing FiO_2 in patients already adequately oxygenated to supranormal values will only increase the physiologically resolved oxygen in plasma, which represents only 2-3% of overall oxygen content. Yet P_aO_2 is the driving force of oxygen flux into the tissue. Significant increases of brain tissue $P_{br}O_2$ after increases of arterial P_aO_2 from normal to supranormal levels have frequently been observed. The P_aO_2 level in arterial blood was linearly related to the $P_{br}O_2$ level in both animal and patient studies.[11,30] The Richmond group has shown that such an increase of brain tissue $P_{br}O_2$ after simply increasing arterial P_aO_2 results in a concurrent decrease of tissue lactate.[27,31] These authors suggest a shift from anaerobic to aerobic metabolism in these injured brains owing to the influence of supranormal levels of P_aO_2. A potential disadvantage of increasing arterial P_aO_2 to very high levels could be a reduction in CBF due to flow regulatory mechanisms [32] , but it seems unlikely that this will be of clinical concern as tissue oxygenation is improved. The potentially harmful effects of FiO_2 levels higher than 60% for longer than 24 hours prohibit long term use of this treatment.

In our opinion sufficient pathophysiological evidence exists to warrant targeting therapy for patients with severe head injury toward improvement of cerebral oxygenation, guided by continuous monitoring of cerebral $P_{br}O_2$. We do not wish to debate extensively the relative value $P_{br}O_2$ measurements and jugular oximetry, but we believe that the two techniques yield complementary information and should preferably be used in conjunction with each other.

3.5 Conclusions

Continuous measurement of cerebral oxygenation, by means of an intra-parenchymally placed Clark type catheter, is a technically reliable, clinically applicable, and, in our experience, safe technique.
Stabilization of the probe/tissue interface can be obtained within a maximum of 2 hours after placement of the catheter. If the probe is inserted in undamaged brain tissue local $P_{br}O_2$ values can be considered representative of larger areas of undamaged tissue, as opposed to insertion of the probe in the so-called "penumbra zone", in which it can be considered indicative of oxygenation of tissue at risk.
Hypoxia of relatively undamaged brain tissue, as evidenced by low $P_{br}O_2$ recordings, is frequent in the first 24 hours after head injury. The depth and duration of local tissue hypoxia are independently related to outcome at 6 months. In patients with severe head injury it may be appropriate to focus intensive care management not only on CPP but, more specifically, on attempts to increase brain tissue oxygen levels. Research concerning the intensive care of patients with severe head injury should focus on the potential clinical benefit of brain tissue oxygen management.

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CHAPTER 4

Brain Tissue Oxygen Response in Severe Traumatic Brain Injury

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Acta Neurochirurgica 145: 429-438,2003

Abstract

*Objective:*To investigate clinical relevance and prognostic value of brain tissue oxygen response (TOR: response of brain tissue PO_2 to changes in arterial PO_2) in traumatic brain injury (TBI).

*Patients and Methods:*In a prospective cohort study TOR was investigated in 41 patients with severe TBI (Glasgow Coma Score ≤ 8) in whom continuous monitoring of brain tissue oxygen pressure ($P_{br}O_2$) was performed. TOR was investigated each day over a five day period for 15 minutes by increasing FiO_2 on the ventilator setting. FiO_2 was increased directly from baseline to 1.0 for a period of 15 minutes under stable conditions (145 tests). In 34 patients the effect of decreasing P_aCO_2 was evaluated on TOR by performing the same test after increasing inspiratory minute volume on the ventilator setting to 20% above baseline. Arterial blood gas analysis was performed before and after changing ventilator settings. Multimodality monitoring, including $P_{br}O_2$ was performed in all patients. Outcome at six months was evaluated according to the Glasgow Outcome Scale. For statistical analysis the Mann-Whitney U- test was used for ordinally distributed variables, and the Chi-square test for categorical variables. Predictive value of TOR was analyzed in a multivariable model.

*Results:*145 tests were available for analysis. Baseline $P_{br}O_2$ varied from 4.0 to 50 mmHg at P_aO_2 values of 73-237 mmHg. At FiO_2 settings of 1.0 $P_{br}O_2$ varied from 9.1-200 mmHg and P_aO_2 from 196-499 mmHg. Three distinct patterns of response were noted: response type A is characterized by sharp increase in $P_{br}O2$, reaching a plateau within several minutes; type B by the absence of a plateau, and type C by a short plateau phase followed by a subsequent further increase in $P_{br}O2$. Patterns characterized by a stable plateau (type A), considered indicative of intact regulatory mechanisms, were seen more frequently from 48 hours after injury on. If present within the first 24 hours after injury such a response was related to more favorable outcome (P=0.06). Mean TOR of all tests was 0.73 ± 0.59 with a median TOR of 0.58. Patients with an unfavorable outcome had a higher TOR (1.03 ± 0.60) during the first 24 hours, compared to patients with a favorable outcome (0.61 ± 0.51; P=0.02). Multiple logistic regression analysis supported the independent predictive value of tissue oxygen response for unfavorable outcome (odds ratio 4.8). During increased hyperventilation mean TOR decreased substantially from 0.75 ± 0.54 to 0.65 ± 0.45 (P=0.06; Wilcoxon test). Within the first 24 hours after injury a decrease in TOR following hyperventilation was significantly related to poorer outcome (P=0.01).

*Conclusions:*Evaluation of TOR affords insight in (disturbances in) oxygen regulation after traumatic brain injury, is of prognostic value and may aid in identifying patients at (increased) risk for ischemia.

Keywords**:** traumatic brain injury, brain tissue PO2, cerebral oxygenation, arterial PO_2, hyperventilation, pathophysiology; ischemia, outcome, prognosis.

4.1 Introduction

Treatment of patients with severe traumatic brain injury (TBI) is directed at prevention, early detection and treatment of secondary insults due to extra- and/or intracranial causes.[1,2] Secondary insults, such as arterial hypoxia, hypotension, elevated Intracranial Pressure (ICP) and low Cerebral Perfusion Pressure (CPP) can be detected with conventional monitoring techniques, including pulse oximetry, intra-arterial blood pressure monitoring (ABP) and ICP monitoring. The importance of monitoring Cerebral Blood Flow (CBF) and cerebral oxygenation is increasingly recognized as cerebral ischemia is considered a key factor in the development of secondary brain damage after TBI. As yet, there are no techniques routinely available for continuous monitoring of CBF. Intermittent measurements may be obtained with stable xenon CT scanning. Transcranial Doppler (TCD) techniques afford the possibility for continuous measurements of flow velocity through the basal arteries of the brain, thereby providing indirect information on CBF.[3,4,5] Cerebral oxygenation may be monitored by jugular bulb oximetry (SjO_2) or by direct measurement of the local brain tissue partial pressure of oxygen ($P_{br}O_2$). Jugular oximetry yields information on global oxygen extraction by the brain.[6,7,8,9,10,11] In contrast, $P_{br}O_2$ monitoring is a local technique, also permitting the opportunity for direct measurements in the penumbra of a lesion, considered at increased risk for ischemia. Previous studies have shown the clinical relevance and prognostic value of monitoring local oxygen tension in brain tissue as parameter for cerebral oxygenation. Low values in the initial 24 hours after injury are significantly associated with poorer outcome.[12,13,14,15,16,17,18]
In cerebral monitoring additional information may be obtained by “challenging the system”. Testing volume pressure response yields information on the reserve capacity of the intracranial compartment to compensate for small volume changes.[19,20] By changing the arterial partial pressure of carbon dioxide (P_aCO_2) changes in ICP and in flow velocity in the basal cranial arteries can be evaluated. Changes in flow velocity induced by changes in P_aCO_2 are closely related to alterations in CBF. Loss of CO_2 reactivity is a negative prognostic factor in patients with severe TBI.[21,22,23,24,25,26,27] Less is known about oxygen regulatory mechanisms in healthy brain and of possible disturbances of these in injured brain.[28,29,30,31] In the normal situation oxygen regulatory mechanisms will be active, maintaining PO_2 in the brain tissue between certain levels: tissue oxygen response (TOR) is expected to be low. In pathological conditions this regulatory mechanism may be disturbed resulting in a more pronounced increase of $P_{br}O_2$ in response to increased arterial partial pressure of oxygen P_aO_2 . Results of preliminary studies supported this hypothesis.[17]
The aim of the underlying study was to “challenge the oxygen regulatory system” by investigating TOR, defined as the change in $P_{br}O_2$ in response to changes in P_aO_2, in patients with severe TBI. We hypothesis the rate of disturbance in tissue oxygen response (TOR) correlates with outcome six months after injury. Higher TOR values were expected in patients with an unfavorable outcome, compared to those with a favorable outcome. The study further focuses on variations of response over time and investigates the influence of decreasing P_aCO_2 on TOR.

4.2 Material and Methods

Patient population

Fourty-one patients with a severe TBI (GCS ≤ 8) were prospectively studied. The study population forms part of a larger series from which the results of brain tissue oxygen monitoring have been reported.[16] The research protocol was approved by the institutional review board and informed consent was obtained from relatives of all participating patients. Mean age was 33 ± 16 years, with a mean GCS after resuscitation of 5.9 ± 1.6. Outcome was evaluated according to the Glasgow Outcome Scale Score (GOS) six months after injury. Patient characteristics are summarized in table 1.
All patients were treated according to a standard protocol, conforming to principles described in the European Brain Injury Consortium (EBIC) guidelines.[32] This included rapid detection and evacuation of intracranial mass lesions, treatment of sustained raised ICP and maintenance of adequate CPP.

Table 1. Characteristics of patient population.

Number of patients	41	
males	35	(85%)
age (mean ± std)	33 ± 16	
GCS (mean ± std)	5.9 ± 1.6	
GCS 3-5	16	(39%)
GCS 6-8	25	(61%)
Outcome 6 months		
Unfavorable outcome	22	(54%)
Death	15	(37%)
Vegetative	0	(0%)
Severely disabled	7	(17%)
Favorable outcome	19	(46%)
Moderate disability	4	(10%)
Good recovery	15	(36%)

GCS = Glasgow Coma Score

Monitoring

Invasive arterial blood pressure (mABP), ICP, CPP (CPP=mABP-ICP), arterial oxygen saturation by pulse oximetry (S_aO_2), End-tidal CO_2 and $P_{br}O_2$ were continuously monitored.
ICP was monitored with a fiberoptic device (Camino lab., San Diego, USA). $P_{br}O_2$ was monitored with a Clark type electrode (Licox, GMS, Germany) positioned in the frontal white matter. ICP and $P_{br}O_2$ catheters were introduced through a modified intracranial bolt in an undamaged part of the frontal lobe, preferably on the right side.

Monitoring was started as soon as possible after admission, with an intended duration of five days. $P_{br}O_2$ monitoring was prematurely ended by early death, or if ICP monitoring was no longer clinically indicated.

Challenging the system: Tissue Oxygen Response

In 41 patients 172 TOR tests were performed. FiO_2 was increased from baseline directly to 1.0 for a period of 15 minutes under stable conditions. At the start and at the end of the 15-minute period all monitored parameters were noted and blood gas analysis was performed. All tests were scrutinized for artifacts. 27 Tests were rejected for analysis, because of unstable hemodynamic or pulmonary conditions, leaving 145 tests available for analysis.
In 34 out of these 41 patients (98 tests) the influence of decreasing P_aCO_2 was evaluated on TOR. Following the initial TOR test and a subsequent stabilization period of 15 minutes, P_aCO_2 was reduced by increasing the inspiratory minute volume by 20%. After a 15-minute stabilization period, the TOR test was repeated. At the end of every step a blood gas analysis was performed and all parameters were noted.

Calculation of Tissue Oxygen Response

Increasing FiO_2 may result in different changes in P_aO_2 in individual patients. It was considered appropriate to relate the change in $P_{br}O_2$ to the change per torr in P_aO_2: The absolute tissue oxygen response (TOR) can be calculated according to the formula:

$$\frac{\Delta P_{br}O_2}{\Delta P_aO_2} = \frac{P_{br}O_2\,(100\%) - P_{br}O_2\,(\text{baseline})}{P_aO_2\,(100\%) - P_aO_2(\text{baseline})}$$

In this formula the absolute changes in $P_{br}O_2$ are related to the absolute changes in P_aO_2. However the degree to which changes of $P_{br}O_2$ can be induced, may depend on baseline values. To correct for this possible effect the change in $P_{br}O_2$ relative to baseline value per torr change of P_aO_2 was calculated. This relative response was defined as:

$$\frac{\Delta P_{br}O_2}{\Delta P_aO_2} \times \frac{1}{P_{br}O_2\,(\text{baseline})} \times 100\%$$

We decided to use the relative TOR for further analysis for two reasons:
A.Theoretically the degree to which changes in $P_{br}O_2$ may be effected following increase of P_aO_2 may be supposed to be dependent on baseline $P_{br}O_2$ values. In earlier studies we have shown that low $P_{br}O_2$ values occur frequently during the first 24 hours increasing to higher or even supranormal levels at 24 to 36 hours after

injury.[16,17] Relating TOR to the baseline $P_{br}O_2$ is therefore considered appropriate.
B.Empirically the relative TOR value is a much stronger predictor for outcome six months after injury than the absolute TOR value. We will further present values for relative response as TOR.

Statistical analysis

All values are presented as mean ± standard deviation. If patients were tested more than once during a certain time period the mean of those tests was calculated and used for analysis (aggregation of values per patient). For comparison of ordinally distributed variables the Mann Whitney U test was used, for categorical variables a Chi-square test was used. Paired values were compared with a Wilcoxon test. The prognostic value of TOR was determined by correlating outcome with clinical and CT- variables in a linear logistic regression model (SPSS Software V9, SPSS Inc. Chicago Ill. USA). P-values ≤ 0.05 were considered statistically significant.

4.3 Results

Tissue Oxygen Response: changes over time and relation to other parameters

Mean TOR of all tests was 0.73 ± 0.59 (range 0 – 2.9) with a median TOR of 0.58

Table 2. Tissue Oxygen Response and outcome.

		Outcome 6 months after injury:		
	All patients	Unfavorable	Favorable	P
	N = 41	N = 22	N = 19	
hrs. after injury	mean TOR (± std)	mean TOR (± std)	mean TOR (± std)	
0-120	0.73 ±0.59	0.78 ± 0.61	0.68 ± 0.57	0.27
0-12	0.64 ± 0.43(22)	0.83 ± 0.46(11)	0.45 ± 0.30(11)	0.02
13-24	1.08 ± 0.82(17)	1.37 ± 0.77(7)	0.88 ± 0.82(10)	0.08
0-24	0.82 ± 0.59(30)	1.03 ± 0.60(15)	0.61 ± 0.51(15)	0.02
25-48	0.83 ± 0.66(30)	0.73 ± 0.60(15)	0.92 ± 0.72(15)	N.S.
49-72	0.62 ± 0.46(28)	0.71 ± 0.57(15)	0.52 ± 0.29(13)	N.S.
73-96	0.59 ± 0.61(25)	0.59 ± 0.62(15)	0.60 ± 0.62(10)	N.S.
97-120	0.65 ± 0.36(12)	0.64 ± 0.32(6)	0.66 ± 0.43(6)	N.S.

Relation between mean TOR ± std at different time periods after injury and outcome at 6 months. The numbers between brackets denote the number of patients studied at different time intervals. P-values relate to differences in TOR between patients with favorable and unfavorable outcome (Mann Whitney U test); N.S. = Not Significant.

(table 2). A strong correlation between absolute and relative O_2 response was found, with Pearson correlation coefficients between 0.57 and 0.88 for the various time periods after injury.
Regression analysis of TOR showed limited dependency of TOR to other measured parameters such as post resuscitation GCS, age, ICP, CPP, mABP and baseline P_aCO_2. Only age, ICP and CPP showed a weak but statistically significant association with TOR (Pearson correlation coefficients 0.20, 0.28 and -0.24 respectively).

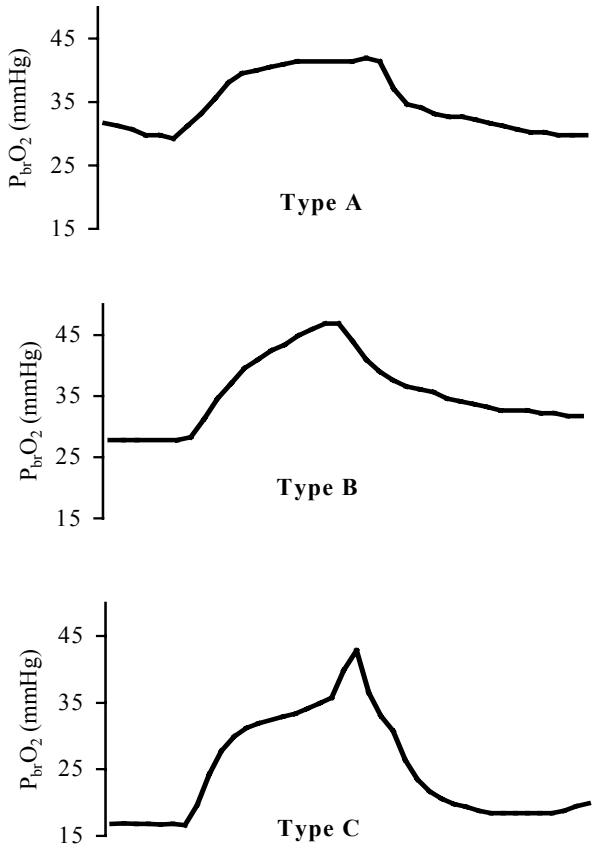

Figure 1. Real time brain tissue PO_2 tracing during a "one-step" TOR tests. After increasing FiO_2 from 0.4 to 1.0 three different types of response curves are observed: Type A: a sharp increase in $P_{br}O_2$ reaching a plateau within several minutes. Type B: a sharp increase of $P_{br}O_2$, followed by a more gradual increase of $P_{br}O_2$ without reaching a plateau within 15 minutes. Type C: a sharp increase of $P_{br}O_2$ followed by a short plateau phase and a subsequent sudden increase in $P_{br}O_2$, suggestive of a "break through phenomenon".

Pattern of response

A total of 120 $P_{br}O_2$ tracings were available for analysis from the 145 "one-step" TOR tests performed in 41 patients. Analysis showed three distinct types of response patterns:
A: a sharp increase of $P_{br}O_2$ on increased FiO_2, reaching a plateau within several minutes.
B: a sharp increase of $P_{br}O_2$ on increased FiO_2, followed by a more gradual increase of $P_{br}O_2$ without reaching a plateau within 15 minutes.
C: a sharp increase of $P_{br}O_2$ on increased FiO_2 followed by a short plateau phase and a subsequent sudden increase in $P_{br}O_2$, suggestive of a "break through phenomenon".
Examples of each response pattern are shown in fig. 1. In 5 tests (5 patients) the response pattern could not be classified according to the patterns identified.
Response pattern A (46 = 40%) and B (51 = 44%) were observed most frequently. Response pattern C was noted in 18 tests in 12 patients. The distribution of the response patterns changed markedly during the days after trauma (table 3). Curve types B and C, e.g. patterns without a plateau, were more common in the first two days after trauma (73 and 76% for day 1 and 2), curve type A was more frequently seen after the first 48 hours after trauma (50, 58 and 67% for day 3, 4 and 5 after trauma). Differences in occurrence of these patterns between day 1, 2 and day 3, 4, 5 were statistically significant (P=0.006, Chi-square test). A strong tendency was noted towards more favorable outcome if curve type A was observed in the first 24 hours (P=0.06): on day 1 curve type A was observed only once in patients with an unfavorable outcome and seven times in patients with favorable outcome. Curve types B and C were observed equally frequent in both groups (11 times each).

Table 3. Frequency distribution of curve patterns in "one-step" TOR tests.

Time period	Curve type A N (%)	B N (%)	C N (%)	No. tests	No. patients
all (N) (%)	46 (40%)	51 (44%)	18 (16%)	115	37
0-24 h	8 (27%)	15 (50%)	7 (23%)	30	25
25-48 h	7 (23%)	16 (53%)	7 (23%)	30	25
49-72 h	11 (50%)	10 (45%)	1 (5%)	22	21
73-96 h	14 (58%)	8 (33%)	2 (8%)	24	22
97-120 h	6 (67%)	2 (22%)	1 (11%)	9	9

Number and percentage of tests is given for the whole group ("all") and for the different time periods after trauma. For description of the different curve types see text and fig. 2.

Tissue Oxygen Response in relation to outcome

During the first 24 hours after injury TOR was significantly lower in patients with a favorable outcome compared to patients with an unfavorable outcome. Differences were most obvious during the first 12 hours after injury. During the subsequent

days after injury no significant differences in TOR between the two outcome groups were noted. In patients with a favorable outcome, TOR increased during the second 24 hours after injury, in contrast to patients with an unfavorable outcome in whom TOR decreased in this period (table 2).
The odds ratio for unfavorable outcome was 4.8 (95% CI: 0.9-25) and for mortality 2.8 (95% CI: 0.7-11). Logistic regression analysis supported the independent prognostic value of TOR as correction for GCS, age, ICP and baseline $P_{br}O_2$ did not clearly alter the odds ratio (table 4).

Table 4. Prognostic value of Tissue Oxygen Response.

	Outcome 6 months after injury	
	Unfav./Fav. Odds ratio (95% CI)	Death/Alive Odds ratio (95% CI)
Tissue Oxygen *Response*	4.8 (0.9-25)	2.8 (0.7-11)
Corrected for:		
age	4.0 (0.8-21)	2.4 (0.6-10)
GCS	5.0 (0.9-28)	2.7 (0.7-11)
ICP	4.4 (0.6-32)	2.1 (0.5-10)
$P_{br}O_2$(baseline)	7.7 (1.1-55)	3.0 (0.7-14)
Combinations:		
All	7.3 (0.7-81)	2.1 (0.4-12)

Odds ratios for unfavorable outcome and for death, and 95 % Confidence Intervals (95% CI) in analysis of prognostic value of TOR versus 6 month outcome for:
- uncorrected TOR during the first 24 hours after injury,
- TOR during the first 24 hours after injury corrected for age, GCS, ICP and $P_{br}O_2$(baseline) and for the combination of these parameters.

Effect of increased hyperventilation on Tissue Oxygen Response

Ninety-eight paired TOR tests in 34 patients were compared during baseline and hyperventilatory conditions (fig. 2). Mean P_aCO_2 during baseline conditions was 33 ± 3 mmHg and during increased hyperventilation 29 ± 3 mmHg ($P < 0.0001$; Wilcoxon test).
Mean TOR decreased substantially from 0.75 ± 0.54 during base-line conditions to 0.65 ± 0.45, during increased hyperventilation (P=0.06; Wilcoxon test). During increased hyperventilation, ICP was reduced significantly compared to normo-ventilatory conditions, though CPP did not increase.
In patients with an unfavorable outcome the difference in TOR between baseline ventilatory conditions and increased hyperventilation was more pronounced. Mean TOR during base-line conditions was 0.80 ± 0.59 (19 patients) which decreased to 0.67 ± 0.49 during increased hyperventilation (P=0.03; table 5).
To further analyze the influence of increased hyperventilation on TOR as prognostic parameter during the first 24 hours after injury a dichotomy was made

Table 5. Influence of (increased) hyperventilation on Tissue Oxygen Response differentiated to outcome.

Unfavorable outcome (N=19)			
	Standard ventilation	Increased hyperventilation	P
TOR ($mmHg^{-1}$)	0.80 ± 0.59	0.67 ± 0.49	0.03
P_aCO_2(mmHg)	32 ± 3	29 ± 3	0.0001
ICP(mmHg)	19 ± 8	16 ± 9	0.004
CPP(mmHg)	84 ± 13	84 ± 16	0.41
$P_{br}O_2$ baselin (mmHg)	26.5 ± 10.5	23.8 ± 8.5	0.0008
Favorable outcome (N=15)			
	Baseline	Increased hyperventilation	P
TOR ($mmHg^{-1}$)	0.69 ± 0.49	0.62 ± 0.40	0.78
P_aCO_2(mmHg)	34 ± 2	30 ± 2	0.0007
ICP(mmHg)	11 ± 6	10 ± 5	0.06
CPP(mmHg)	87 ± 13	88 ± 10	0.22
$P_{br}O_2$ baseline (mmHg)	26.8 ± 8.4	24.1 ± 8.2	0.001

Mean values ± std for TOR, P_aCO_2, ICP and CPP during baseline conditions and at increased hyperventilation differentiated to outcome. P-values determined by Wilcoxon tests.

into "responders" and "non-responders". "Responders" were defined as patients with a change in TOR from baseline to increased hyperventilation of more than 0.10 $mmHg^{-1}$. Of 24 patients studied during this time period, 10 were "responders" and 14 were "non-responders". In the "responders" 8 out of 10 had an unfavorable outcome and in the "non-responders" only 4 out of 14 (P=0.01; Chi-square Z = 6.2; table 6).

Beyond 24 hours after injury there was a trend to more favorable outcome in non-responders, but differences were not significant.

Table 6. Early TOR response to hyperventilation and outcome.

	Outcome 6 months		
	Unfavorable	Favorable	Total
Responders (Δ TOR > 0.10)	8	2	10
Non responders (Δ TOR ≤ 0.10)	4	10	14
Total	12	12	

Dichotomy in patients who respond with a reduction in TOR to hyperventilation of ≤ 0.10 and > 0.10 according to outcome 6 months after injury, during the first 24 hours. (P=0.01, Chi-square test).

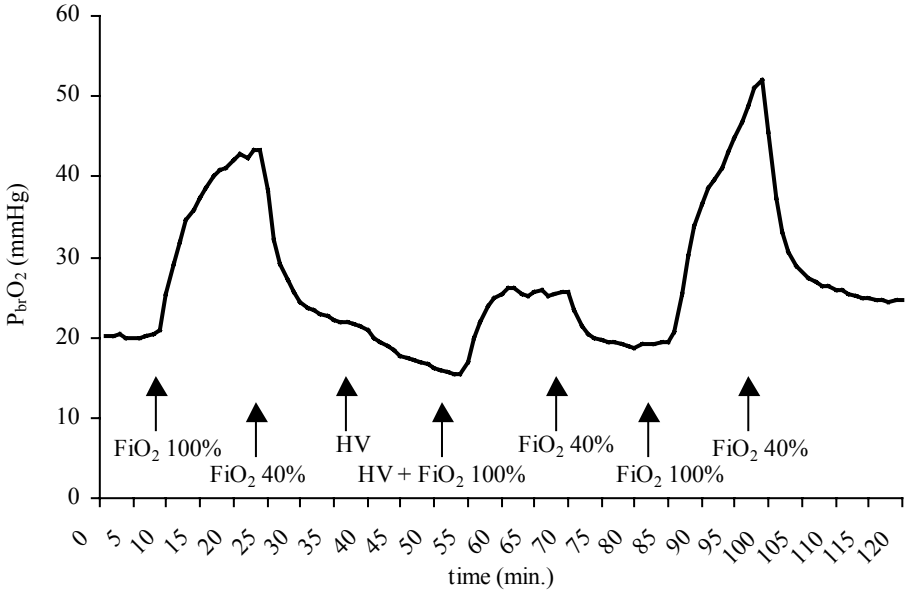

Figure 2. Real time brain tissue PO_2 tracing during a "one-step" TOR, followed by a 15 minute period for equilibration. Subsequently increased hyperventilation is instituted by increasing the inspiratory minute volume (IMV) by 20%, followed by a second "one-step" TOR test during increased hyperventilatory conditions. After this procedure a third "one-step" TOR test during baseline conditions is performed. Arrows indicate changing FiO_2 and IMV levels (HV = increased hyperventilation).

4.4 Discussion

Previous studies have shown the feasibility and clinical relevance of monitoring brain tissue PO_2.[16, 17] Despite some disadvantages, inherent to a local method, $P_{br}O_2$ may be considered to reflect global brain oxygenation if the catheter is placed in a relatively undamaged region. Depth and duration of low $P_{br}O_2$ values during the first 24 hours after injury correlate with death and unfavorable outcome at six months.[16] If positioned in the "penumbra" area of a contusion, $P_{br}O_2$ monitoring may further aid in guiding therapy, aimed at rescuing potentially salvageable tissue. In this study we address a hitherto relatively unexplored field in monitoring cerebral oxygenation: "Challenging the system" by increasing FiO_2, and evaluation of the influence on brain oxygen tension. The field is intriguing for three reasons: 1) Assessment of Oxygen regulatory mechanisms, 2) Evaluation of possible therapeutic efficacy of increasing FiO_2 to prevent/treat brain ischemia, 3) Prognostic implications.

Regulatory mechanisms

Secondary insults after brain injury are common, and have an adverse effect on outcome. Under normal conditions different (auto)regulatory mechanisms are active to prevent cerebral ischemia following secondary insults. Many regulatory mechanisms at cellular and tissue level in the brain exist. Clinically the most important are autoregulation of cerebral blood flow [33], pressure compensating mechanisms [19,34] and CO_2 reactivity.[29,30] In TBI regulatory mechanisms may be impaired and consequently adverse effects of secondary insults are more pronounced in a brain rendered vulnerable due to the primary injury.

In healthy individuals autoregulatory mechanisms operating through changes in the precapillary resistance vessels maintain CBF within normal limits at mABP levels ranging from 50 to 150 mmHg.[33] In patients with impaired autoregulatory mechanisms, due to TBI, CBF is more dependent on CPP. This constitutes one of the rationales for CPP therapy, but it is recognized that in individual patients it is difficult to determine the appropriate level of CPP required to maintain adequate tissue perfusion and oxygenation.[8,35]

Cerebral blood vessels are also responsive to changes in arterial CO_2 pressure (P_aCO_2), the so-called CO_2 reactivity. In normal situations CO_2 reactivity causes a change of CBF of 3-4% per torr change in P_aCO_2.[3,25] This mechanism is mediated by changes in extracellular pH. On decreasing P_aCO_2 (hypocapnia) vasoconstriction is induced and Cerebral Blood Volume (CBV) decreased, leading to a reduction in ICP. How strong this effect may be in individual patients is difficult to determine. Following severe TBI cerebral arteriolae may loose their capacity to react to changes in P_aCO_2, especially during the first 24 hours after injury [36], but CO_2 reactivity is preserved longer than flow autoregulation. Loss of CO_2 reactivity is correlated with poor outcome.[24, 26, 37]

Less is known about possible O_2 regulatory mechanisms. Kety and Schmidt [30] showed in healthy volunteers that CBF changes markedly in relation to changes in arterial O_2 content. Inhalation of high oxygen mixtures (FiO_2 between 85 and 100%) reduced CBF with an average of 13%. Inhalation of gas mixtures with 10 % oxygen induced an average increase in CBF of 35%. Other studies confirmed these observations.[28, 31] It may be concluded that the cerebral resistance vessels are influenced by arterial O_2 tensions, maintaining the Cerebral Metabolic Rate of oxygen at constant levels. It can therefore be assumed that under normal conditions oxygen regulatory mechanisms are operative and that cerebral oxygenation is maintained within normal ranges, largely independent of P_aO_2. Indeed, in animal experiments we demonstrated that during hyperoxia, increasing P_aO_2 from 125 ± 8 mmHg to 282 ± 22 mmHg, Cerebrospinal Fluid (CSF) PO_2 increased only by 20%, and that at higher P_aO_2 levels CSF PO_2 showed only small further increases.[38] These observations were considered further evidence of oxygen regulatory mechanisms. If such oxygen regulatory mechanisms are active, it may be presumed that TOR under normal conditions, will be relatively low. This hypothesis is supported by recent animal experiments (table 7), which show a low mean TOR value in healthy swine.[39, 40, 41] In the clinical situation, evidence for impairment of O2 regulatory mechanisms has previously been reported by Meixensberger et al.

[42] in patients undergoing surgical procedures for an intracranial tumor or cerebrovascular disorder. Upon increasing FiO2 to 1.0 they found an increase of $P_{br}O2$ of 352% in pathological cortex versus 138% in normal cortex.
Even less is known about possible disturbances in oxygen regulatory mechanisms in patients with severe TBI. We previously reported preliminary results on TOR in a study of 22 patients with TBI, increasing FiO_2 stepwise from baseline to 1.0.[17] In contrast to our findings in non-traumatized animals in the experimental situation, this study demonstrated a linear relation between P_aO_2 and $P_{br}O_2$ in patients with TBI, extending also into regions of high P_aO_2. The slope of the regression line varied within patients at different time periods, and also between patients. We further found an association between unfavorable outcome and higher TOR. The observed linear relation between $P_{br}O_2$ and P_aO_2 in patients with TBI and the association of higher TOR with unfavorable outcome imply that O_2 regulatory mechanisms are impaired in TBI.
In the current study it was considered appropriate to perform a "one-step" test instead of a "multi-step" test as we had previously demonstrated the linear relation in patients with TBI. The patterns of response distinguished during these one-step O_2 reactivity tests may also reflect the extent of impairment of oxygen regulatory mechanisms.
The occurrence of response type A, characterized by a sharp increase of $P_{br}O_2$ on increasing FiO_2 , reaching a plateau within several minutes, may be considered evidence of establishment of a new equilibrium in response to regulatory mechanisms. The absence of such a plateau, as in response type B, or the observation of a so-called "break through" phenomenon, as in response pattern C, may be considered evidence of impairment of oxygen regulatory mechanisms. The observed trend that outcome is more favorable in patients with response pattern A during the first 24 hours after injury is in agreement with this hypothesis. A serious limitation, prohibiting definite conclusions however, is that we could not continuously monitor arterial PO_2 , and thus cannot exclude the possibility that observed patterns merely reflect pulmonary conditions influencing gas exchange. Future studies will be directed to this issue.
Further limitation of our study is that no conclusions can be drawn concerning regulatory mechanisms in TBI patients during systemic hypoxia, as the lowest P_aO_2 values observed were 73 mmHg at baseline situations and 196 mmHg at FiO_2 100%.

Prognostic implications

We hypothesize that the degree of impairment of oxygen regulatory mechanism is related to the severity of injury, and that higher TOR levels may be expected in patients with poorer outcome. Our results confirm this hypothesis and conclusions are further supported by results from other studies (table 7). Menzel et al. [43] reported a higher TOR in patients with unfavorable outcome following TBI compared to those with a favorable outcome (0.9 ± 0.6 versus 0.4 ± 0.16). Fandino et al. [44] and Longhi et al. [45] found mean TOR values comparable to our data in

pathological circumstances. Recalculating data from Rossi et al. [41] with the TOR formula used by us, TOR is inversely related to CBF in a swine model.
We found that patients with an unfavorable outcome after TBI had a higher TOR and differences were statistically significant during the first 24 hours after trauma. The absence of statistical significance in later time periods may be due to smaller number of patients studied in these periods, exclusion of patients dying early, or be reflective of a similar functioning of oxygen regulatory mechanisms in both outcome groups. Supportive for the last argument is that in the group of patients with a favorable outcome TOR increases to values which were found in the group with an unfavorable outcome. Beyond 48 hours after trauma TOR returns in both outcome groups to values which are found immediately after trauma in the group with a favorable outcome. Possibly these values represent close to normal TOR values. In the study performed by Fandino et al. [44] no correlation was observed between TOR and outcome. This can be explained by the relatively small study group, but probably more important is that none of the patients were studied within the early phase after trauma. This explains the slightly lower mean TOR, because the higher values in our study were observed during the initial period after trauma. Results obtained in our previous study in which TOR was studied with a "multi-step"test and the results of the current study are in concordance.
On pooled analysis of the 64 patients TOR was significantly related to mortality (OR 3.8 CI: 1.1-14).
The higher TOR observed in patients with an unfavorable outcome may possibly be explained by mitochondrial dysfunction [46,47], causing incapability of complete utilization of provided oxygen. Alternatively it may be considered evidence of more pronounced vasoparalysis, with a consequently increased "catchment area", resulting in higher measured $P_{br}O_2$ values as P_aO_2 increases. Physiologic determinants of the "catchment area"of the oxygen probe include the number, diameter and spatial distribution of microvascular vessels. Tissue oxygenation results both from diffusion at the capillary interface as from direct diffusion to cells along the arterioles.[48] In the presence of functional shunting to venules through a variety of mechanisms [49] an additional contribution may result from diffusion along venules. Consequently measured PO_2 values may be presumed to be influenced by vascular diameter and degree of functional shunting, resulting from microcirculatory disruption. At increased arterial PO_2 these factors may bias the electrode values to higher levels.[48] We hypothesize that TOR testing in TBI yields information on the severity of microcirculatory disruption.

Hyperventilation and TOR

The observation that TOR is significantly depressed, following even small reductions of P_aCO_2 is of interest. One explanation could be that reduction of P_aCO_2 restores vascular tone and as such may be considered beneficial. Alternatively, as reduction of P_aCO_2 results in vasoconstriction, the depressed TOR following increased hyperventilation, may be indicative of a critical reduction of vessels contributing to oxygenation in the "catchment area" of the catheter. As such, the

Table 7. Tissue oxygen response under normal and pathological conditions (literature studies)

Author and year of publication	TOR*	Population (Number of subjects studied)
Experimental studies		
Manley et al. 1999 [39]	0.32	healthy swine (N=8)
Menzel et al. 2000 [40]	0.21	healthy piglets (N=7)
Rossi et al. 2001 [41]	0.16	healthy swine (N=7)
	0.4	swine with 50-60% CBF
	0.52	swine with 20-30% CBF
Clinical studies		
Van Santbrink et al. 1996 [17]	0.73 ± 0. 48	TBI patients (N=22)
	0.94 ± 0. 48	unfavorable outcome
	0.55 ± 0. 41	favorable outcome
Fandino et al. 1999 [44]	0.6	TBI patients (N=9)
Menzel et al. 1999 [43]	0.7	TBI patients (N=14)
	0.9	unfavorable outcome
	0.4	favorable outcome
Longhi et al. 2002 [45]	0.73	comatose patients(N=20)

*TOR recalculated from data in manuscript according to the formula:

$$\frac{\Delta P_{br}O_2}{\Delta P_aO_2} \times \frac{1}{P_{br}O_2} \times 100\%$$

observation of reduced O_2 reactivity following increased hyperventilation may be considered indicative of a critical state of tissue perfusion and oxygenation. The observation that outcome is significantly poorer in patients demonstrating decreased TOR following increased hyperventilation, favors this explanation. If these observations can be replicated in future studies the therapeutic implications are major: on basis of a combination of TOR testing and the influence of decreasing P_aCO_2 on TOR, patients at risk for ischemia may be identified. It may be expected that especially these patients may benefit from therapy targeted at improvement of cerebral oxygenation. Conversely, institution of hyperventilation in these patients may be contra indicated because of an adverse influence.

Towards oxygen targeted therapy

Therapeutic strategies aimed at improving oxygenation may consist of increasing oxygen content of the arterial blood, or by improving delivery through increase of flow. Correcting anemia and ensuring optimal saturation of the arterial blood is the most important method for improving oxygen content of the arterial blood. Increasing FiO_2 in patients already adequately oxygenated will increase P_aO_2 considerably, but the net effect on arterial oxygen content is small. Despite this we have shown that increasing FiO_2 and consequently P_aO_2 leads to a significant increase of $P_{br}O_2$. Microdialysis studies performed by Menzel et al. [43] show a concurrent decrease in tissue lactate in the brain, following increase of FiO_2. These

observations support the rationale for increasing $P_{br}O_2$ through manipulations of FiO_2 and targeting therapy towards cerebral oxygenation.

4.5 Conclusions

We conclude that in monitoring of cerebral oxygenation, procedures for "challenging the system" and determination of TOR yields important additional information. Results, by necessity, remain tentative because the number of patients is limited and the data are heterogeneous and require confirmation in future studies. On basis of TOR studies the possibility exists for targeting therapy aimed at the improvement of cerebral oxygenation to the appropriate population. Furthermore patients may be identified in whom hyperventilation is possibly contra-indicated.
TOR is a strong independent prognostic indicator within the first 24 hours after injury. In conjunction with results from our studies on monitoring cerebral oxygenation, the results of this work further identify the first 24 hours as a critical period in patients with a severe TBI.

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CHAPTER 5

CO_2 Reactivity and Brain Oxygen Pressure Monitoring in Severe Head Injury

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Crit Care Med 28(9): 3268-3274,2000

Abstract

*Objective:*To investigate the effect of hyperventilation on cerebral oxygenation after severe head injury.

*Design:*A prospective observational study.

*Setting:*Neuro intensive care unit at a university hospital.

*Patients:*A total of 90 patients with severe head injury (GCS ≤ 8), in whom continuous monitoring of brain tissue oxygen pressure ($P_{br}O_2$) was performed as measure of cerebral oxygenation.

*Interventions and measurements:*Arterial PCO_2 was decreased each day over a five day period for 15 minutes by increasing minute volume on the ventilator setting to 20% above baseline. Arterial blood gas analysis was performed before and after changing ventilator settings. Multimodality monitoring including $P_{br}O_2$ was performed in all patients. Absolute and relative $P_{br}O_2/P_aCO_2$ reactivity was calculated. Six month outcome was evaluated, according to the Glasgow Outcome Scale.

*Main results:*Effective hyperventilation, defined by a decrease of $P_aCO_2 \geq 2$ mmHg, was obtained in 218 (84%) of 272 tests performed. Baseline P_aCO_2 averaged 32.3 ± 4.5 mmHg. Average reduction in P_aCO_2 was 3.8 ± 1.7 mmHg. $P_{br}O_2$ decreased by 2.8 ± 3.7 mmHg ($p < 0.001$) from a baseline value of 26.5 ± 11.6 mmHg. $P_{br}O_2/P_aCO_2$ reactivity was low on day 1 (0.8 ± 2.3 mmHg), increasing on subsequent days to 6.1 ± 4.4 mmHgon day 5. $P_{br}O_2$ /P_aCO_2 reactivity on days 1 and 2 was not related to outcome. In later phases in patients with unfavorable outcome relative reactivity was increased more markedly reaching statistical significance on day 5.

Conclusions:(Increased) hyperventilation causes a significant reduction in $P_{br}O_2$, providing further evidence for possible increased risk of secondary ischemic damage during hyperventilation. The low $P_{br}O_2/P_aCO_2$ reactivity on day 1 indicates decreased responsiveness of cerebral microvascular vessels to P_aCO_2 changes, caused by generalized vascular narrowing. The increasing $P_{br}O_2/P_aCO_2$ reactivity from day 2 to 5 suggests that the risk of compromising cerebral oxygenation by hyperventilation may increase over time.

Keywords: head injury, brain tissue PO_2, hyperventilation, cerebral oxygenation, arterial PCO_2, pathophysiology, ischemia, therapy, outcome, prognosis.

5.1 Introduction

Cerebral ischemia is recognized as one of the main factors involved in the development of secondary brain damage after severe head injury. Therapeutic approaches aim at prevention of secondary insults and maintenance of adequate Cerebral Blood Flow (CBF) and oxygenation. In the uninjured brain, coupling exists between CBF and metabolic demands, and CBF is maintained within required ranges independent of physiologic variations in blood pressure and viscosity; these autoregulatory functions are controlled by alterations in Cerebral Vascular Resistance (CVR), effected by changes in the diameter of precapillary resistance vessels.[1,2,3] Cerebral blood vessels are also responsive to changes in arterial CO_2 pressure (P_aCO_2), the so-called CO_2 reactivity. This mechanism is mediated by changes in extracellular PH.[3] On increasing P_aCO_2, tissue acidosis results, causing vasodilatation and reduction of CVR, leading to an increase in CBF and Cerebral Blood Volume (CBV). On decreasing P_aCO_2 (hypocapnia), vasoconstriction is induced and CBV decreased, leading to a reduction in Intracranial Pressure (ICP). This reduction in CBV, and consequently ICP, forms the rationale for the use of hyperventilation in the treatment of raised ICP.[4] The risk of this approach however is induction or exacerbation of ischemia, caused by reduced CBF.[5,6,7] Consequently the use of hyperventilation in severe head injury is currently considered controversial [7,8,9,10,11,12] and when institution of hyperventilation to levels below a P_aCO_2 of 30 mmHg is instituted, monitoring of cerebral oxygenation or CBF is recommended.[13] For this purpose jugular oximetry is advocated, which allows for continuous monitoring of jugular venous oxygen saturation (SjO_2) and calculation of the arterio-venous oxygen content difference ($AVDO_2$). [14,15,16] The technique of continuous SjO_2 monitoring is however prone to technical artifacts and methodological errors and may potentially underestimate the occurrence of regional ischemia.[17,18]

Clinical studies in patients with head injury from our group have shown the feasibility of continuous monitoring of local brain oxygen pressure ($P_{br}O_2$) as a parameter for cerebral oxygenation.[19,20] $P_{br}O_2$ is considered to reflect the net balance between oxygen supply and demand at the tissue level.[21] Despite the limitations of such a local method, studies have shown results to be indicative of global cerebral oxygenation when monitoring is performed in a relatively undamaged part of the brain.[22,23,24,25] Low $P_{br}O_2$ values were frequently seen within the first 24 hours after head injury, indicative of early ischemia and their occurrence has been shown to be related to poor outcome.[19]

The aim of the current study was to investigate the effect of hyperventilation on $P_{br}O_2$ in a standardized way, to investigate whether such effect differs over time, and to evaluate whether continuous $P_{br}O_2$ monitoring indicate impending ischemia for increasing hyperventilation.

5.2 Materials and Methods

Patient population

From September 1992 to September 1997, the effect of reducing P_aCO_2 on $P_{br}O_2$ ($P_{br}O_2/P_aCO_2$ reactivity) was studied in 90 patients with severe nonpenetrating head injury (GCS ≤ 8), admitted to the neuro-intensive care unit of the University Hospital Rotterdam. In 10 patients the initial GCS was > 8, but later deteriorated to coma. Eighty-four patients were admitted to the study within 24 hours after trauma, and six between 24 and 52 hours. The main characteristics of the patient population are summarized in table 1.

The research protocol was approved by the institutional review board and informed consent obtained from relatives of all participating patients. Monitoring procedures included heart rate, arterial oxygen saturation (SaO_2) with pulse oximetry, End-tidal CO_2, ventilatory parameters and respiratory rate, mean arterial blood pressure (mABP), ICP, cerebral perfusion pressure (CPP) and $P_{br}O_2$. ICP was monitored intra-parenchymally with a fiberoptic catheter (Camino, San Diego, USA).

Treatment was aimed at rapid detection and evacuation of intracranial mass lesions, treatment of raised ICP and maintenance of adequate CPP, conforming to principles described in the guidelines of the European Brain Injury Consortium.[26] All patients were intubated and artificially ventilated. Patients were sedated with Midazolam, administered either by continuous infusion or intermittent boluses. For analgesia fentanyl or morphine was given. Paralytic agents were not routinely used. In the majority of patients (85%) the initial ventilator settings were in a volume control mode. Respiratory rate and inspiratory time were adjusted to

Table 1. Patient characteristics

Mean age	35 ± 17 (range 11-83)%
Male	76%
Median admission GCS	6
Normal pupil reactivity	45 (50%)
Dilated nonreactive pupils	9 (10%)
Unilateral nonreactive pupil	36 (40%)
Preadmission hypotension	11 (13%)
Preadmission hypoxia	15 (17%)
Intracranial mass lesions	
Epidural hematoma	12
Acute subdural hematoma	23
Intracerebral hematoma	8
Contusion	18
Extra cranial injuries	62 (69%)
% Favorable outcome at 3 months	41%
% Favorable outcome at 6 months	48%

GCS = GlasgowComaScale

maintain peak pressure levels below 30-40 cm H_2O. A 40% fraction of inspired oxygen (FiO_2) was sufficient to ensure adequate oxygenation ($P_aO_2 \geq 100$ mmHg) in 90% of patients. Raised ICP above levels of 20-25 mmHg were, after exclusion of operable lesions, treated in a staircase fashion with mannitol infusions, mild to moderate hyperventilation and as a last resort, barbiturates (18 patients). CPP was maintained above levels of 60 mmHg with intravascular volume expansion and if necessary vasopressor therapy (35% of patients).

$P_{br}O_2$ monitoring

$P_{br}O_2$ was measured with a polarographic Clark type electrode, connected to a Licox monitoring device (GMS, Kiel, Germany). The catheter was inserted through a three-way skull bolt, allowing for simultaneous introduction of the fiberoptic ICP catheter and the $P_{br}O_2$ catheter. The catheters were inserted in the frontal region, contralateral to the main injury, preferably on the right side. Catheter specific calibration settings were installed according to the manufacturer's specifications. Monitoring procedures were started as soon as possible after ICU admission, with an intended duration of five days. $P_{br}O_2$ monitoring was prematurely ended by early death or if ICP monitoring was no longer clinically considered indicated. After removal of the catheters post-measurement calibration was performed in 80 patients. All parameters obtained from the multimodality monitoring were digitally stored as an average minute by minute value with a custom developed software package (CDAI, University Hospital Rotterdam).

Interventions: Manipulation of P_aCO_2

To investigate $P_{br}O_2$/ $P_aCO_2$reactivity, (increased) hyperventilation was induced by increasing minute volume on the ventilator setting to 20% above baseline for a period of 15 minutes. Mode of ventilation, level of PEEP and respiratory frequency were not changed. For ethical reasons no paralytic agents were administered for the purpose of the investigations. If the peak pressure values on the ventilator increased to more than 40 mmHg, or if ICP increased to levels above 25 mmHg, the test was prematurely ended (five patients). Prior to changing the ventilator settings and after 15 minutes of (increased) hyperventilation, arterial blood samples were obtained for blood gas analysis. Reactivity tests were performed when possible daily during the initial five days after trauma, under relatively stable conditions of the patients during which periods no nursing procedures were performed or treatment changed. The mean number of tests per patient was 3.

Calculation of CO_2 reactivity

Increasing minute volume by 20% may result in variable changes in P_aCO_2 in individual patients. It was therefore considered appropriate to calculate the change of $P_{br}O_2$ per torr change of P_aCO_2 . This calculated parameter may be termed the absolute reactivity and is defined as:

$$\frac{\Delta P_{br}O_2}{\Delta P_aCO_2} = \frac{P_{br}O_2 \text{ baseline} - P_{br}O_2 \text{ hyperv.}}{P_aCO_2 \text{ baseline} - P_aCO_2 \text{ hyperv.}}$$

The degree to which changes of $P_{br}O_2$ can be induced by hyperventilation may be dependent on baseline values. Baseline $P_{br}O_2$ levels have been shown to increase in the initial 24 to 36 hours after trauma.[19] To correct for this possible effect the change of $P_{br}O_2$ relative to baseline value per torr change of P_aCO_2 was calculated. This parameter may be termed the relative reactivity and is defined as:

$$\frac{\Delta P_{br}O_2}{\Delta P_aCO_2} \times \frac{1}{P_{br}O_2 \text{ baseline}} \times 100\%$$

Outcome

Outcome was evaluated at six months after trauma, according to the Glasgow Outcome Scale (GOS).[27] For prognostic analysis the GOS was dichotomized into unfavorable outcome (dead, vegetative, severe disability) versus favorable outcome (moderate disability plus good recovery).

Statistical analysis

Results are expressed as means ± std. Student's T-tests were utilized to evaluate differences between normally distributed contiguous parameters. If normal distribution could not be assumed, as was the case in analysis of changes over time, a Kruskal Wallis one way analysis of variance on the ranks was performed, followed by the Dunn's method for an all permissive multiple comparison. Instat (Inc. CA, USA) and SPSS 7.0 (Inc. Chicago, USA) software were used for data processing and analysis.

5.3 Results

$P_{br}O_2$ monitoring, distribution and effectiveness of procedures

Monitoring was initiated on average 7 hours after trauma. The average duration of monitoring was 92 hours (range 5-196 hours). No hemorrhage or infections related to catheter introduction and monitoring occurred during the study. Postmeasurement calibration showed a zero drift of 0.5 ± 0.7 mmHg and an average sensitivity drift of –0.5 ± 10 mmHg.

Increasing minute volume on the ventilator settings was not successful in decreasing arterial P_aCO_2 in all patients, mainly because some patients were on synchronized intermittent mandatory ventilation (SIMV) mode. Effective

Table 2. Distribution of tests over 5-day study period.

Hours after Trauma	No. of tests Effective Hyperventilation (ΔP_aCO_2, ≥ 2 mmHg)	Noneffective Hyperventilation (ΔP_aCO_2,<2mmHg)
0-24	68	10
24-48	49	13
49-72	43	11
73-96	37	13
96-110	21	7
total	218	54

hyperventilation was defined as a decrease of 2 mmHg or more in P_aCO_2. As such effective hyperventilation was obtained in 218 (80%) of the 272 reactivity tests performed under stable conditions. Due to various reasons (unstable condition, early death, premature discontinuation of monitoring, organizational aspects) daily measurements could not be performed in all patients. The distribution of tests per 24 hour period and the effectiveness of hyperventilation are summarized in table 2. No significant differences concerning baseline values were present between tests where hyperventilation was effective or not (table 3).

Table 3. Baseline values in effective vs. noneffective hyperventilation tests.

	Effective Hyperventilation (218 tests)	Noneffective hyperventilation (54 tests)
$P_{br}O_2$	26.5 ± 11.6	26.6 ± 9.3
P_aCO_2	32.3 ± 4.5	32 ± 4.22
ΔP_aCO_2	3.8 ± 1.7	1.3 ± 0.4*
ICP	18.6 ± 11.1	17.9 ± 13.1
MABP	97.4 ± 12.6	98.8 ± 13.7
P_aO_2	136 ± 40.9	121.1 ± 34.4

*P <0.05

Effect of decreasing P_aCO_2 on brain tissue oxygen tension

Increasing minute volume by 20% resulted in an average reduction of P_aCO_2 of 3.3 ± 1.8 mmHg ($P < 0.0001$). ICP was reduced from 18.4 ± 11.5 mmHg to 15.3 ± 10.6 mmHg ($P < 0.0001$).

Increased hyperventilation caused an average reduction of $P_{br}O_2$ from 26.5 ± 11.6 at baseline to 23.6 ± 10.6 mmHg ($P < 0.0001$). A decrease in $P_{br}O_2$ was noted in 84% of the 218 tests in which hyperventilation was effective (mean 2.8 ± 3.7 mmHg), but also in 94% of the 54 tests (mean 2.2 ± 2.7 mmHg), in which increased

Table 4. Time course of CO_2 reactivity

Time period (Day)	No.	$P_{br}O_2$ (mean ± Std)	$\Delta P_{br}O_2$ (mean ± Std)	P_aCO_2 (mean ± Std)	ΔP_aCO_2 (mean ± Std)
1	68	21.8 ± 12	0.8 ± 2.3	32.7 ± 4.8	4.1 ± 1.6
2	49	30.4 ± 11[a]	2.3 ± 3.6	31.0 ± 3.4	3.6 ± 1.4
3	43	28.3 ± 11[b]	3.9 ± 3.1	31.6 ± 4.0	3.5 ± 1.1
4	37	27.0 ± 10	4.1 ± 4.1	32.9 ± 4.8	3.7 ± 1.3
5	21	27.1 ± 11	6.1 ± 4.4	34.2 ± 5.2	4.4 ± 3.4

[a] $P_{br}O_2$ day 1 vs. day 2, P<.0001; [b] day 1 vs. day 3, P<.005

ventilation was not effective in reducing P_aCO_2 by more than 2 mmHg. $P_{br}O_2$ decreased during procedures to levels below 20 mmHg in 23 tests from 20 patients, to levels below 15 mmHg in five tests from five patients and to levels below 10 mmHg in 14 tests from eight patients. Such reduction to levels possibly considered critical occurred in 35% of patients within the first 24 hours, probably reflecting the lower $P_{br}O_2$ values occurring in the early phase after trauma.

Time course of CO_2 reactivity

The effect of P_aCO_2 reduction on $P_{br}O_2$ was strongly influenced by the time period during which studies were performed. In patients in whom effective hyperventilation was obtained, an average decrease of $P_{br}O_2$ of 0.8 ± 2.3 mmHg was noted on day 1, increasing to 6.1 ± 4.4 mmHg on day 5 (P < 0.0001). Results are summarized in table 4. The adverse effect of increased hyperventilation on

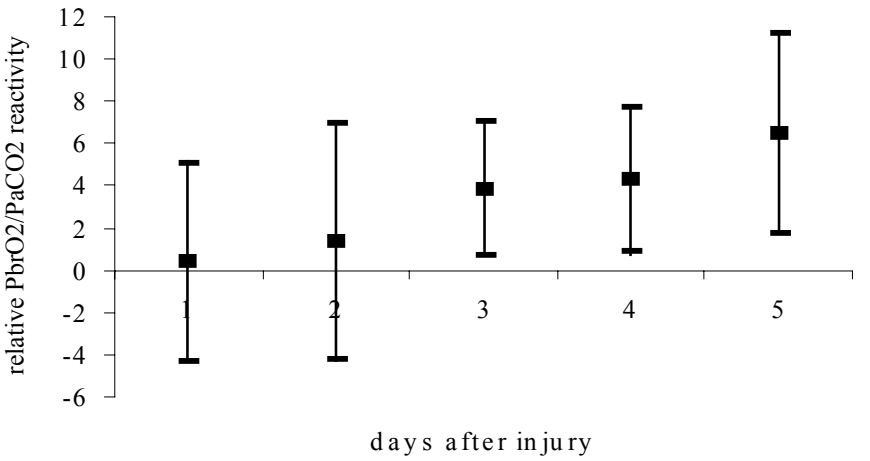

Figure 1. Time course of relative $P_{br}O_2/P_aCO_2$ reactivity in a cohort of 21 patients, studied over the full 4-5 day monitoring period. Mean ± std.

$P_{br}O_2$ increases over time, while differences in P_aCO_2 reduction were similar between time periods. To exclude possible influences of changing numbers of patients per period we studied a cohort of 21 patients was studied in whom serial studies were available over the full four to five day monitoring period. Results did not differ from the overall trends shown in table 4, as illustrated in figure 1.

Calculation of $P_{br}O_2/P_aCO_2$ reactivity

CO_2 reactivity on $P_{br}O_2$, both absolute and relative, was low on day 1 and progressively increased over time. Results are shown in table 5.

Table 5. Absolute and relative brain tissue oxygen pressure P_aCO_2 reactivity.

Time period (Day)	No.	Absolute Reactivity (mean ± Std)	Relative Reactivity (mean ± Std)
1	68	0.2 ± 0.7	0.4 ± 4.7
2	49	0.7 ± 1.1	1.4 ± 5.6[a]
3	43	1.2 ± 1.0[b]	3.9 ± 3.2[b]
4	37	1.1 ± 1.1[b]	4.3 ± 3.4[b]
5	21	1.7 ± 1.7[b]	6.5 ± 4.7[b]

[a]Day vs. day 5, $P < .01$; [b]day 1 vs. day 3,4 or 5, $P < .001$

On day 1 absolute reactivity was below 1.0 in 91% of tests performed and on day 4/5 in only 38 % of tests. Statistical analysis showed relative CO_2 reactivity on $P_{br}O_2$ to be significantly higher on days 2 through 5 in comparison to day 1. Relative reactivity on day 5 was significantly higher than on day 2 ($P < 0.001$). Significant results were also obtained for the absolute reactivity. An approximately linear relation between calculated absolute and relative reactivity is shown in figure 2. The correlation coefficient comparing the two calculations of reactivity was 0.83.

CO_2 reactivity in relationship to baseline P_aCO_2

We studied patients with a widely varying baseline PCO_2 (range 23.9 - 48 mmHg). Because results of CO_2 reactivity tests could potentially be influenced by the level of initial P_aCO_2 before performing the test, we evaluated whether results of the reactivity tests were dependent on initial P_aCO_2.
To this purpose, patients were divided into three groups:
baseline $P_aCO_2 \leq 30$ mmHg: moderate hyperventilation (34% of tests),
P_aCO_2 30-35 mmHg: mild hyperventilation (34% of tests),
baseline $P_aCO_2 \geq 35$ mmHg: normoventilation (28% of tests).
Because of the low number of tests per group in the latter time period, results from days 2 to 3 and from days 4 to 5 were analyzed together. If multiple tests were performed within these time periods in individual patients, results were averaged. Increasing minute volume by 20% resulted in a larger decrease of P_aCO_2 in patients with normoventilation over all time periods as compared with those with mild or moderate hyperventilation. On day 1, this difference was statistically significant. In

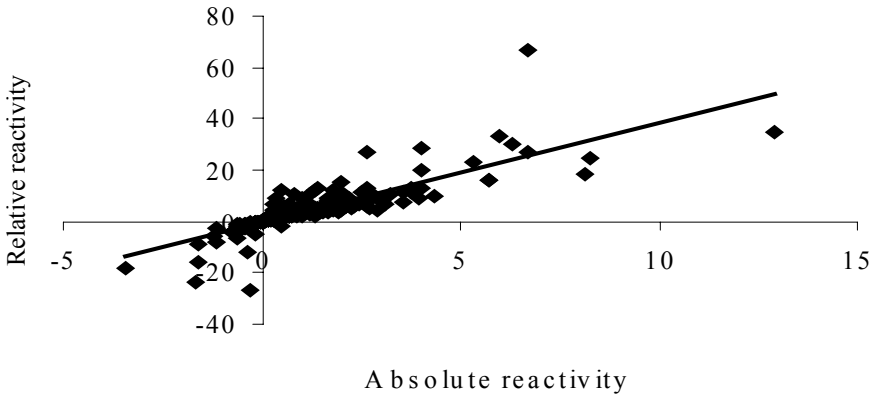

Figure 2. Correlation between calculated values for absolute and relative reactivity obtained from 218 $P_{br}O_2/P_aCO_2$ reactivity tests.

patients with normoventilation Δ P_aCO_2 was 4.93 ± 2.1 and in patients with moderate hyperventilation 3.55 ± 1.1 ($P < 0.02$). Baseline $P_{br}O_2$ was comparable between the three groups (day 1: 19.7-22.1 mmHg, day 2/3; 27.8-29.4 mmHg, day 4/5: 25.5-29.7 mmHg). Results on calculated $P_{br}O_2/P_aCO_2$ reactivity are shown in table 6.

No significant differences between groups were found. It is noteworthy however that in patients initially hyperventilated, relative reactivity increased from day 2/3 to day 4/5, a phenomenon which was not observed in the normoventilated patients.

$P_{br}O_2/P_aCO_2$ reactivity in relation to outcome

No significant differences on $P_{br}O_2/P_aCO_2$ reactivity were noted on day 1 and 2 between patients with unfavorable or favorable outcome. However, calculated values for absolute and relative reactivity increased in patients with unfavorable outcome from day 3 on, and relative reactivity was significantly higher on day 5. Results are summarized in table 7.

Table 6. Results of calculated brain tissue oxygen pressure P_aCO_2 reactivity.

	Moderate hyperventilation		Mild hyperventilation		Normoventilation	
	Absolute	Relative	Absolute	Relative	Absolute	Relative
Day	Reactivity	Reactivity	Reactivity	Reactivity	Reactivity	Reactivity
1	0.4 ± 0.8	0.6 ± 5.9	0.1 ± 0.7	1.0 ± 4.4	0.0 ± 0.5	-0.3 ± 3.2
2/3	0.8 ± 0.9	2.8 ± 2.3	0.9 ± 1.1	1.8 ± 6.8	1.3 ± 0.9	3.7 ± 3.3
4/5	1.6 ± 1.1	4.5 ± 4.6	1.7 ± 1.6	6.1 ± 4.4	0.8 ± 0.7	3.4 ± 2.6

5.4 Discussion

Hyperventilation and the risk of ischemic damage

Hyperventilation is still generally considered a cornerstone therapy in the management of raised ICP and in patients with severe head injury.[4, 12, 13] Hyperventilation is routinely used in 83% of centers in the US [28] and in 89% of centers in the UK and Ireland.[29] In 57% of these centers the treatment aim was to decrease arterial PCO_2 to levels below 30 mmHg. In the evidence-based recommendations of the US guidelines [13] it is stated as a standard, based on Class I evidence that prolonged hyperventilation should be avoided in the absence of increased ICP. The use of hyperventilation as an adjunct measure for brief intervals in the management of raised ICP remains acceptable. Although beneficial in reducing ICP, the risk of hyperventilation is the induction of ischemic damage.
Hyperventilation reduces ICP by vasoconstriction and subsequent reduction in cerebral blood volume and CBF. In healthy volunteers Raichle et al. [6] describe a 40% decrease in CBF, 30 minutes after decreasing P_aCO_2 by 15 to 20 mmHg. The response however was transitory and after four hours CBF was restored to 90% of baseline values.[6] Clinical studies in patients with severe head injury have shown a 3% change in CBF per mmHg change in P_aCO_2, but the response is lower in patients with lower CBF.[30] In the first 24 hours after trauma low CBF values occur frequently, down to levels of 20-30 ml/100 g/min in the first four to eight hours.[31, 32] Any further reduction of CBF in these critical phases may be

Table 7. Brain tissue oxygen pressure P_aCO_2 reactivity and outcome.

Day	GOS 6 months: Unfavorable No.	Absolute Reactivity	Relative Reactivity	GOS 6 months: Favorable No.	Absolute Reactivity	Relative Reactivity
1	34	0.3 ± 0.7	1.0 ± 3.6	34	0.1 ± 0.6	-0.1 ± 5.6
2	28	0.6 ± 1.4	0.8 ± 7.2	21	0.7 ± 0.8	2.2 ± 2.2
3	23	1.3 ± 1.0	4.1 ± 2.8	20	1.1 ± 0.9	3.7 ± 3.7
4	20	1.4 ± 1.2	5.2 ± 3.4	17	0.8 ± 0.9	3.3 ± 3.2
5	10	1.8 ± 0.9	8.4 ± 4.1[a]	11	1.7 ± 2.2	4.8 ± 4.7

GOS, Glasgow Outcome Scale.
[a]$P < .01$.

considered hazardous, as the risk for secondary ischemic damage is increased. Hypocapnia has been identified as one of the main causes of desaturation episodes detected by jugular venous saturation monitoring.[14,15]
Our studies show a decrease of brain tissue oxygen pressure in 84% of patients with severe head injury following only small reductions of P_aCO_2. As such the results provide further proof of the potential risk of increasing secondary ischemic damage at larger reductions of P_aCO_2 caused by inadvertent or therapeutically instituted

hyperventilation. Serial studies performed over five days after trauma show a progressively increasing reactivity over time, indicating that the risk of reducing oxygen supply by hyperventilation may also increase over time. Conversely however, it may not be concluded that hyperventilation is a relatively safe procedure in the first 24 hours. Low baseline values of $P_{br}O_2$ occur predominantly in this period and it is at this time that patients are at risk for ischemic damage. We have further shown that particularly in this period even small reductions in P_aCO_2 may decrease $P_{br}O_2$ to levels considered critical, i.e. to levels below 15 mmHg.

Interpretation of $P_{br}O_2$ measurements and CO_2 reactivity

Brain tissue oxygen pressure is supposed to reflect the balance between oxygen supply and demand at the tissue level. Normal values of $P_{br}O_2$ obtained with the technique employed will be difficult to ascertain in humans. Based on animal experiments and clinical experience values of 20-30 mmHg may be considered normal. Oxygen supply is determined by the arterial oxygen content and CBF. Over the relatively short time periods during which the studies were conducted no clear changes occurred in arterial PO_2, arterial blood pressure or hemoglobin concentration. Consequently any observed reduction in $P_{br}O_2$ on decreasing P_aCO_2 may be supposed to be caused by a reduction in CBF. This is supported by the results of a small study reported by Doppenberg et al. [23], describing a strong correlation between CBF and $P_{br}O_2$ monitored with the Paratrend® sensor. In a study on transcranial Doppler and $P_{br}O_2$ in 17 patients with head injury Dings et al. [24] showed the flow velocity in the middle cerebral artery to decrease concurrently with a reduction in $P_{br}O_2$ after induced hypocapnia.
Some reservations concerning the interpretation of the $P_{br}O_2$ measurements and $P_{br}O_2/P_aCO_2$ reactivity studies are however appropriate. In the technique of $P_{br}O_2$ monitoring employed, the polarographic O_2 sensitive electrode averages the local PO_2 values from the "catchment area" surrounding the probe. Measured values are therefore dependent not only on the flow, but also on the number and diameter and spatial distribution of local microvascular vessels.[22, 33] It may be supposed that the low or absent $P_{br}O_2/P_aCO_2$ reactivity, observed in the first 24 hours after trauma, are indicative of vascular narrowing, either due to vasoconstriction caused by a direct effect of trauma or secondary to transient metabolic depression [34], or vasocompression possibly caused by swelling of the astrocytic foot processes.[35] In such a state of vascular narrowing reduction of P_aCO_2 will not be able to further decrease the diameter of cerebral microvasculature. Consequently the results of $P_{br}O_2/P_aCO_2$ reactivity studies might be considered to reflect an indirect measurement of the diameter of cerebral microvascular vessels. The observed increase in $P_{br}O_2/P_aCO_2$ reactivity over time may therefore reflect a progressive vasodilation of these vessels. Whether this is a local phenomenon, or reflects more generalized changes remains a matter of speculation. As it was our intent to perform measurements in a relatively undamaged part of the brain, extrapolation of results as representative of more global values can be justified, with the restriction that in more damaged areas different results could be obtained.

Absolute versus relative reactivity

Absolute reactivity calculates the change in $P_{br}O_2$ per torr change in P_aCO_2. The relative reactivity relates the absolute reactivity to baseline $P_{br}O_2$ values, describing a percentage change. Previous studies from our group have shown low $P_{br}O_2$ values in the first 24 hours after trauma.[19] Baseline $P_{br}O_2$ increases to normal values between 24 and 36 hours after trauma, sometimes exhibiting an overshoot phenomenon to transient supranormal levels. Changes in $P_{br}O_2$ induced by a reduction in P_aCO_2 may be expected to be lower when baseline $P_{br}O_2$ is low. Calculating the relative reactivity corrects for such influences and therefore permits comparison of values over various time periods over which baseline $P_{br}O_2$ differs.
Based on these theoretical considerations the relative reactivity is to be preferred for expressing $P_{br}O_2/P_aCO_2$ reactivity. In practice we have demonstrated a close correlation between absolute and relative reactivity. A further advantage of calculating relative reactivity is that results can be more easily compared to CO_2 reactivity studies on CBF, transcranial Doppler and jugular saturation monitoring. Studies on CBF have shown a relative responsitivity in severe head injury of 3% change in CBF per torr change in P_aCO_2.[31] Transcranial Doppler studies also report a 3% change in flow velocity per torr change in P_aCO_2.[36] These results are very similar to values of relative $P_{br}O_2/P_aCO_2$ reactivity varying between 4 and 7% on days 3 to 5 after injury. Although some reservations concerning such comparison are appropriate, as the different techniques measures different variables, they all relate directly or indirectly to some aspect of CO_2 vasoreactivity.

$P_{br}O_2/P_aCO_2$ reactivity in perspective

Whilst the adverse influence of decreasing P_aCO_2 on CBF and SjO_2 is well documented [7, 8, 14, 15], only few studies are reported investigating the influence of P_aCO_2 changes on $P_{br}O_2$. In a study limited to 17 patients with severe head injury Dings et al. [24] describe increasing reduction of $P_{br}O_2$ observed during serial investigations performed over seven days after injury. This preliminary observation is replicated in our present larger series. In this study also $P_{br}O_2/CO_2$ reactivity was low in the first day after trauma despite a larger CO_2 reduction compared to that effected in our studies. Schneider et al. [25] investigating the influence of hyperventilation on brain tissue PO_2 in 15 patients showed a similar reactivity compared to the values obtained in our studies.
Our study clearly shows a reduction in brain tissue PO_2 in response to reduction in arterial PCO_2. This effect increases as time progresses after injury. Both absolute and relative reactivity are low in the first 24 hours and steadily increase over the five day monitoring period. This time dependent increase can not be explained by different responses in P_aCO_2 reduction obtained, or by changing baseline $P_{br}O_2$ values. Despite the robustness of our results the study may be criticized: only relatively small reductions in arterial PCO_2 were effected and a substantial number of patients (32%) were already hyperventilated to P_aCO_2 levels below 30 mmHg prior to initiating the tests performed. The aim of our studies was to investigate $P_{br}O_2/P_aCO_2$ reactivity in patients with severe head injury without interfering with

clinical management and without exposing patients to additional risks, such as might be incurred with the use of paralytic agents.[37] For these reasons, although desirable from a scientific point of view, paralytic agents were not administered; consequently the procedures followed were not effective in reducing arterial PCO_2 in all patients. The observed average reduction of P_aCO_2 by 3.3 mmHg on increasing minute ventilation by 20% is somewhat smaller than would be expected, especially in patients already hyperventilated at baseline. This may be explained by increased dead air space. For reasons stated we did not aim at a large reduction in arterial PCO_2 and tests were limited to a 15-minute period of increased ventilation. It is conceivable that greater reductions of arterial PCO_2 than obtained in our studies may provoke a more profound decrease in $P_{br}O_2$. Although we calculated values for absolute and relative reactivity no information is available whether $P_{br}O_2$ has a linear relationship to changing P_aCO_2. We could however not find any statistically significant difference in absolute or relative reactivity between patients with intensive, moderate or normoventilation in the various time periods studied.

We would have expected to find some relation between $P_{br}O_2/P_aCO_2$ reactivity and outcome in the early phase after trauma, but were unable to find any statistically significant results. A number of reasons may be considered: the absent, or very low reactivity on day 1 is a general phenomenon occurring in all patients; studies were only performed over a small range of arterial P_aCO_2 and most studies were conducting during a state of mild hyperventilation at baseline. The relatively low number of patients studied may also be important.

The higher reactivity noted on day 4 and 5 in patients with unfavorable outcome may indicate a situation in which, although baseline $P_{br}O_2$ is still normal, cerebral oxygenation is compromised to some degree and that in this situation further vasoconstriction has an adverse influence on tissue oxygenation.

The hypothesis however that $P_{br}O_2/P_aCO_2$ reactivity is dependent not only on CBF, but also on the diameter and number of vessels in the "catchment area" of the probe makes it difficult to draw definite conclusions, but at the same time poses intriguing research questions. Further experimental and clinical studies are required to elucidate the relation between $P_{br}O_2/P_aCO_2$ reactivity and CBF or diameter of pial vessels.

5.5 Conclusions

Despite the uncertainties concerning the interpretation of results we concluded that increased hyperventilation causes a reduction in brain tissue PO_2; this may be considered an adverse phenomenon incurring the risk of secondary ischemic damage, particularly in those patients with compromised cerebral oxygenation as demonstrated by low baseline $P_{br}O_2$ values or results of other studies on cerebral blood flow and oxygenation. This risk would appear highest in the initial 24 hours after trauma when CBF is low; our results further show an abolished or very low $P_{br}O_2/P_aCO_2$ reactivity in this period, indicating an absence of response of cerebral microvascular vessels to P_aCO_2. The value of hyperventilation in this time period may therefore be considered debatable. The increasing $P_{br}O_2/P_aCO_2$ reactivity from

day 2 to 5 suggests that the risk of compromising cerebral oxygenation by hyperventilation increases during this time period.

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CHAPTER 6

$P_{br}O_2$ validation by SPECT

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In preparation.

Abstract

*Introduction:*Local brain tissue partial pressure of oxygen ($P_{br}O_2$) is considered as a global parameter for brain oxygenation if the tip of the catheter is placed in a relative healthy part of the brain. In this study the relation between Cerebral Blood Flow (CBF) in the catheter measurement area and the CBF in the supratentorial region, and between CBF and the local $P_{br}O_2$ value is studied. Besides it is evaluated whether CT scanning alone is appropriate for reliable placement of the $P_{br}O_2$ catheter.

*Methods:*Seventeen severe head injured patients (GCS $\leq$ 8) were prospectively studied. Serial Single Photon Emission Computed Tomography (SPECT) studies were performed on day 1, 6 and 14 after injury and relative CBF values for the catheter area and the global supratentorial region were compared. Macroscopic CBF disturbances on SPECT were compared with macroscopic lesions on CT scanning, with special interest for the $P_{br}O_2$ catheter area. $P_{br}O_2$ was measured intraparenchymatously with a Clark type electrode (Licox). The absolute $P_{br}O_2$ value was related to the relative CBF value.

*Results and Conclusions:*No differences were seen between the calculated relative CBF values for the catheter measurement area and the global supratentorial region. Cerebral damage direct after trauma is adequately diagnosed by CT scanning, and therefore positioning of the $P_{br}O_2$ catheter is reliable with CT scanning alone. The relationship between the absolute $P_{br}O_2$ value and the calculated relative CBF during the first day after trauma is weak.

Keywords: head injury, brain tissue PO_2, SPECT.

6.1 Introduction

Treatment of patients with a severe head injury is based on prevention of secondary insults by intensive monitoring. Monitoring brain tissue partial pressure of oxygen ($P_{br}O_2$) has recently become available as a monitoring tool and seems to be useful in the treatment of patients with a severe head injury.[1,2] One of the major drawbacks of this method is that it measures oxygen partial pressure (PO_2) in a very local part of the brain. Controversy exists whether the catheter has to be placed in a relative healthy part of the brain, "in the penumbra" zone of a lesion or within a lesion. If the catheter is placed in a relative undamaged part of the brain the local PO_2 seems to reflect the whole brain oxygenation. Catheter placement in the penumbra zone of a lesion or in the lesion itself gives lower $P_{br}O_2$ values, and therapy can be directed towards saving this threatened area.[12,13,14]
In this study Single Photon Emission Computed Tomography (SPECT) is used in combination with $P_{br}O_2$ monitoring in a series of patients with a severe head injury. We made the choice to place the $P_{br}O_2$ catheter in a relative healthy part of the brain. The aim of this study is to investigate:
1) Whether the blood flow in the relative undamaged frontal lobe in a patient with a severe head injury is representative for the global supratentorial Cerebral Blood Flow (CBF).
2) Is CT scanning sufficient to decide whether the localisation of the tip of the PO_2 catheter is in an adequate position? And
3) Is the relative CBF (rCBF) in the frontal lobe or the global supratentorial rCBF associated with the absolute $P_{br}O_2$?

6.2 Material and Methods

Patient population

Seventeen patients with a severe head injury (GCS≤8) were prospectively studied. The study population is part of a larger series from which results of $P_{br}O_2$ monitoring have been reported earlier.[1,2] The study protocol was approved by the local ethical committee and informed consent was obtained from relatives of all patients. Mean age was 31 ± 13 years (range 14-73), with a mean post resuscitation GCS score of 6.6 ± 1.6. All demographic data are listed in table 1.
Treatment was aimed at rapid detection and evacuation of intracranial mass lesions. Raised Intracranial Pressure (ICP) and maintenance of adequate Cerebral Perfusion Pressure (CPP), was treated according to a standard protocol, conforming to the principles described in the European Brain Injury Consortium (EBIC) guidelines.[3]

Monitoring

$P_{br}O_2$ was measured with a polarographic microcatheter (Clark type) with a diameter of 0.5 mm and a 5 mm long sensitive area for partial pressure of oxygen,

connected to a Licox® device (GMS, Kiel, Germany). ICP was monitored with a fiberoptic device (Camino lab., San Diego, USA). ICP and $P_{br}O_2$ catheters were introduced through a modified intracranial bolt in the frontal white matter, preferably the right side, unless a large contusion or skull fractures were present at

Table 1. Patient Demographics.

	Mean	±std	Number
Age	31	14	
Male/Female			13/4
Admission GCS	6.6	1.6	
Normal pupil reactivity			11
Unilateral non-reactive pupil			3
Bilateral non-reactive pupils			3
Intracranial mass lesions:			
-Epidural heamatoma			1
-Subdural haematoma			5
-Intracerebral haematoma			1
Favorable/Unfavorable outcome			8/9

the right side, the left side was used (one patient). Data were stored in a custom made data collecting program (CDAI AZR, the Netherlands) with a one minute interval. For calculation of the relationship between $P_{br}O_2$ and rCBF in SPECT studies, the mean $P_{br}O_2$ of one hour before the SPECT study was used.

CT and SPECT protocol

All patients had on admission and approximately 24 hours after admission a CT-scan. Further CT scans were made on indication and 14 ± 1 days after the injury.
SPECT studies were made on day 1, day 6 ± 1 day, and day 14 ± 1 day after injury. In all SPECT studies 740 mBq 99m-Technetium HexaMethyl Propylene Amine Oxime (99m-Tc HMPAO) was used. Twenty minutes after injection data acquisition was started which took on average 40 minutes for 120 projections. These projections were reconstructed to 3 or 6 millimeter thick slices according to the protocol of the Department of Nuclear Medicine. First a Siemens Orbiter camera, matrixsize 64×64, and later a Picker 3 head camera with a matrixsize of 128×128 was used. Analysis of SPECT images was performed by measuring regional HMPAO uptake in 14 regions in the brain. These regions were determined by automatically 3 dimensional image fitting to a normal template based on SPECT studies of 30 healthy volunteers.[4,5] The frontal region ipsilateral to the $P_{br}O_2$ catheter was chosen as region of interest. This region consists 40% of the total hemisferic volume, localised in the frontal portion of the brain. The volume of the infratentorial region is about 5% of the total supratentorial volume.
Analysis of SPECT studies was performed in two ways:

A: rCBF was calculated in the frontal region ipsilateral to the $P_{br}O_2$ catheter (frontal rCBF) and in the total supratentorial region (global rCBF), relating HMPAO uptake in the defined regions to the total infratentorial uptake, assuming that the cerebellar uptake is relatively constant over time.
B: Lesions were visually scored by two of the authors (HvS and JWS) as well in SPECT as CT studies.

Statistics

All values are presented as mean ± standard deviation. Paired values were compared with a paired T-test. For testing the relationship between values, simple linear regression analysis was used (Microsoft Exel 97, USA). A P value ≤ 0.05 was considered statistically significant.

6.3 Results

SPECT studies

In total 42 SPECT studies in 17 patients were performed. Fifteen SPECT studies were performed in the first period after trauma with a mean interval of 18.4 ± 7.0 hours after injury (range 3 – 24 hours). In 14 patients a (second) SPECT study was performed with a mean interval of 5.8 ± 1.0 days after injury (range 5 – 8 days). A third SPECT study was performed in 13 patients with a mean interval of 14.3 ± 1.1 days after trauma (range 13 – 17 days). In three patients only the first study was performed because these patients died between day 1 and 5 after injury. In two patients the first and in one patient the third SPECT study was not performed because of technical problems with the SPECT device.
During all first SPECT studies (15) and in 8 out of 14 patients during the second SPECT study a $P_{br}O_2$ value was obtained. So in 23 SPECT studies a simultaneous $P_{br}O_2$ value was available. In 6 patients no $P_{br}O_2$ value during the second SPECT study was obtained because the study was performed beyond the $P_{br}O_2$ study limit of 120 hours after trauma.

CT studies

In total 58 CT studies in 16 patients were available for analysis. All 16 patients had a CT scan on admission and most patients had a CT scan 24 hours after injury. In 11 patients a CT scan 3 months or later after trauma was available, 3 patients died before this time period and in 2 patients a late CT scan was not available.

Macroscopic visible lesions on CT and/or SPECT

In total 36 macroscopic lesions were visible either on SPECT or CT scanning, of which 19 were visible on both imaging techniques.

In 41 SPECT studies in 16 patients in total 25 regions with macroscopical hypoperfusion were seen, equally divided between both hemisferes. Lesions were most frequently seen in the frontal (7) and the temporal (9) region, only twice a lesion in the occipital region was detected.
58 CT studies in 16 patients showed 30 contusional areas in 13 patients. Three patients had no macroscopical visible contusional areas. Most lesions were observed in the frontal (12) and temporal (11) regions, and no lesions were seen in the occipital region. The contusional areas were equally divided between both hemispheres.
In 2 patients a contusional area on CT was seen close to the $P_{br}O_2$ catheter. In one patient $P_{br}O_2$ was low during the whole period of observation with a mean $P_{br}O_2$ value of 16 mmHg and a minimal $P_{br}O_2$ value of 8 mmHg. In the other patient no abnormal $P_{br}O_2$ values were observed.

Table 2. Macroscopical visible lesions on CT and/or SPECT.

		CT visible		
		Yes	No	Total
SPECT visible	Yes	19	6	25
	No	11	-	11
	Total	30	6	36

Eleven of the 30 lesions seen on CT scaning were not visible on SPECT. Six lesions seen on SPECT were not visible on the CT scan (table 2). Two of these lesions were already visible on the first SPECT study after trauma, 4 lesions in 4 patients appeared on the second or third SPECT study. Three out of 4 of these patients had initially after trauma $P_{br}O_2$ values below 15 mmHg during one or more hours. One patient developed late low values (< 10 mmHg) during a long period, with a mean $P_{br}O_2$ value during the whole observation period of 12.5 mmHg.
In 2 patients 4 hypodense lesions on the CT scan, not related to posttraumatic contusional areas, were observed 3 months after the injury. In one patient one and in the other patient three lesions were observed. Both patients had normal $P_{br}O_2$ values during the whole period of observation, with minimal $P_{br}O_2$ values of respective 18 and 16 mmHg.

Relative CBF

rCBF in the frontal region ($P_{br}O_2$ measurement area)

Mean rCBF in the $P_{br}O_2$ measurement area for all SPECT studies was 0.84 ± 0.22. During the first SPECT study mean rCBF in the $P_{br}O_2$ measurement area was 0.80 ± 0.23, during the second SPECT study 0.92 ± 0.16 and during the third 0.93 ± 0.13 (table 3). In one patient an exceptional low rCBF of 0.17 was found in the $P_{br}O_2$ measurement area with a $P_{br}O_2$ of 10.6 mmHg, during the first SPECT study.

rCBF in the global supratentorial region

Mean rCBF in the supratentorial region for all SPECT studies was 0.89 ± 0,13. During the first SPECT study mean rCBF in the supratentorial region was 0.86 ± 0.14, during the second SPECT study 0.93 ± 0.11 and during the third 0.95 ± 0.12 (table 3).

Relation between rCBF in the $P_{br}O_2$ measurement area and the global supratentorial region

No statistical significant differences were found between the rCBF in the $P_{br}O_2$ measurement area and the rCBF in the global supratentorial region. rCBF values were compared with a paired T test and P values ranged from 0.12 during the first SPECT study to 0. 88 during the second SPECT study.
Correlation coefficient between the rCBF in the $P_{br}O_2$ measurement area and the global supratentorial region for all studies (N=42) was 0.75, during the first SPECT study 0.77 (N=15), during the second 0.71 (N=14) and during the third 0.82 (N=13).(table 3, figure 1)

Table 3. Relative Cerebral Blood Flow values.

	$P_{br}O_2$ measurement area		
	Frontal region	Global supratentorial region	P-value
Mean	0.84 ± 0.22	0.89 ± 0.13	0.12
1st SPECT	0.80 ± 0.23	0.86 ± 0.14	0.12
2nd SPECT	0.92 ± 0.16	0.93 ± 0.11	0.88
3rd SPECT	0.93 ± 0.13	0.95 ± 0.12	0.28

Mean rCBF values for the whole observation period and the different time periods after trauma given in the frontal region ($P_{br}O_2$ probe measurement area) and the global supratentorial region. P values were not significant (paired T test).

Probe positioning; The relation between macroscopical frontal CBF lesions in SPECT and frontal contusions in CT scanning

First SPECT study
In 5 out of 15 patients a macroscopical low CBF was detected at the
probe side in the first SPECT study. In all of these patients a lesion at the probe side on the CT scan was found. In 1 additional patient a frontal contusion at the probe side on the CT scan was seen, without a visible low CBF on the SPECT study.
At the non-probe side, 3 out of 15 patients showed a macroscopical low CBF on the SPECT study. CT scanning showed in 5 out of 15 patients a lesion at the non-probe side, including the 3 patients with a low CBF in SPECT.

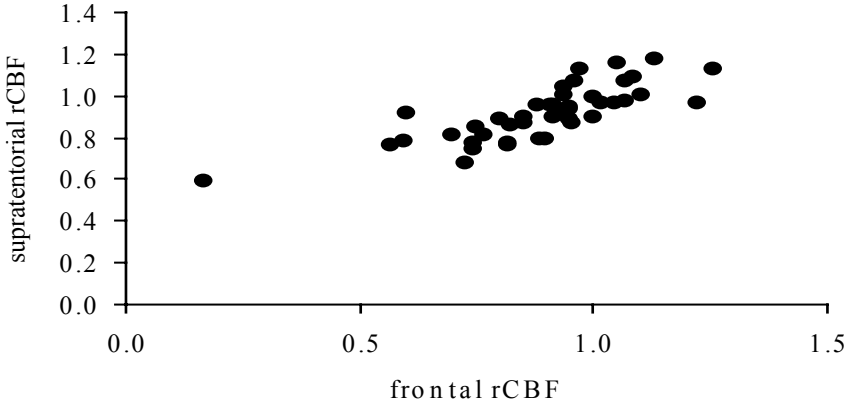

Figure 1. Graph showing the relationship between relative Cerebral Blood Flow (rCBF) in the frontal and the global supratentorial region. All 42 SPECT studies are represented. Pearson correlation coefficient = 0.75.

Second SPECT study

In 4 out of 14 patients a macroscopical low CBF at the probe side in SPECT was found. These lesions were already visible during the first SPECT study. One patient with a low CBF during the first SPECT study died. In 7 out of 14 patients a simultaneous CT study was performed of which 3 with a macroscopical low CBF at the probe side. In 2 out of 3 of these patients a lesion on the CT scan was visible. The fourth patient had no simultaneous CT scan. In one patient a lesion on the CT scan was visible at the probe side without a low CBF on the SPECT study.

At the non-probe side in only 1 out of 14 patients a low CBF was detected, while 4 lesions were seen at the non-probe side with a simultaneous CT scan in 7 patients, including the one seen in the SPECT study.

Third SPECT study

During the third SPECT study in 10 out of 13 patients a simultaneous CT can was performed. In all patients with a macroscopical low CBF on SPECT a lesion on the CT scan was found, except in one patient who developed a delayed low CBF at the probe side no lesion was visible on the CT scan. In one patient with a low CBF on the SPECT study no simultaneous CT study was performed.

At the non-probe side one lesion was seen as well on SPECT as on CT, no other lesions were detected.

During the first period after trauma no macroscopical low CBF in the frontal region ipsi- or contralateral to the probe side was missed by CT studies. Even more lesions were detected with CT scanning than with the early SPECT studies. This is also applicable for the second SPECT study. In only one patient during the third SPECT study a delayed low CBF in the frontal region was found which would have been missed with CT scanning only.

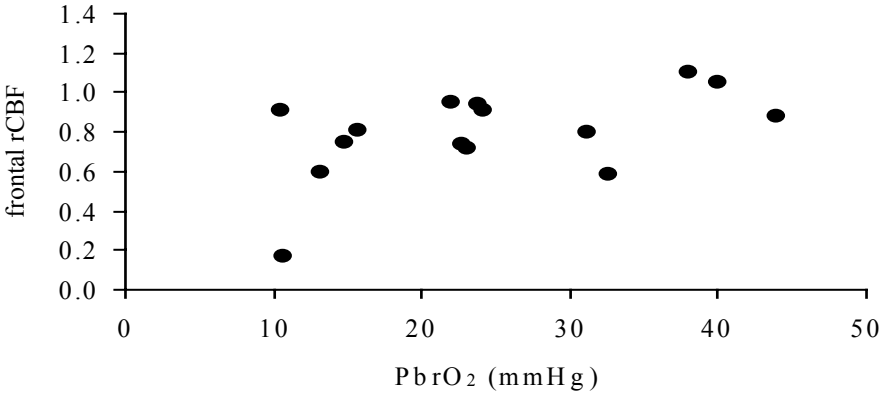

Figure 2. Graph showing the relationship between frontal rCBF and the mean $P_{br}O_2$ of 1 hour before the first SPECT study. 15 studies were performed in this time period. Mean interval between time of injury and SPECT study was 18 ± 7 hours. Pearson correlation coefficient = 0.51.

Relation between $P_{br}O_2$ and rCBF

In 23 SPECT studies a simultaneous $P_{br}O_2$ measurement was available. During the first SPECT study in all 15 patients, during the second SPECT study in 8 patients and during the third SPECT study in none of the patients a simultaneous $P_{br}O_2$ value was available.

$P_{br}O_2$ and frontal rCBF

The correlation coefficient between ipsilateral frontal rCBF and $P_{br}O_2$ in all 23 studies was 0.36 with a P value of 0.09. During the first SPECT study the correlation coefficient between ipsilateral frontal rCBF and $P_{br}O_2$ was 0.51 with a P value of 0.05 (figure 2), during the second SPECT study no relationship existed (figure 3). If a dichotomy was made for patients with a $P_{br}O_2 \leq 15$ mmHg and without and with a frontal rCBF of ≤ 0.75 and without, a tendency towards low $P_{br}O_2$ values in combination with low frontal rCBF values was found though it reached no statistical significancy. This tendency was most prominent when only the first SPECT study was taken into account.
No distinct differences in relationship between frontal rCBF and $P_{br}O_2$ were detected as a subdivision was made in patients who had a macroscopic low CBF in SPECT and a visible lesion on CT (N=5) or a visible lesion on CT without a macroscopic low CBF on SPECT (N=1) and patients who had no visible lesions. Mean $P_{br}O_2$ in patients with a visible lesion on the CT scan was 22.5 mmHg and in patients without a visible lesion 25.1 mmHg.

Patients in which the first SPECT study was performed within 12 hours after trauma (N=3) showed no distinct relationship between frontal rCBF and $P_{br}O_2$ compared to the whole group.
Patients who showed a low $P_{br}O_2$ (below 10 or 15 mmHg during one or more hours) during the first 24 hours after trauma showed no different relationship between $P_{br}O_2$ and frontal rCBF than patients who had no initial low $P_{br}O_2$ values.

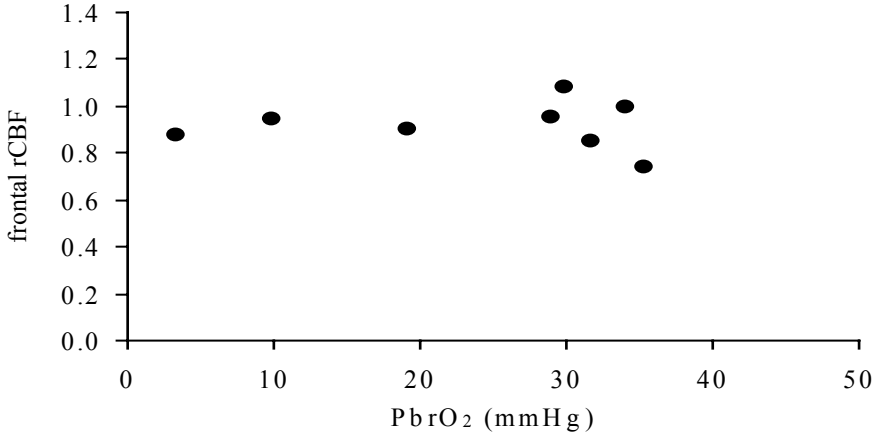

Figure 3. Graph showing the relationship between frontal rCBF and the mean $P_{br}O_2$ of 1 hour before the second SPECT study. 8 out of 14 SPECT studies that were performed in this time period had a simultaneous $P_{br}O_2$ value. Mean interval between time of injury and SPECT study was 5.8 ± 1 days. No significant correlation could be found.

$P_{br}O_2$ and global supratentorial rCBF

No statistical significant relationship could be found between global supratentorial rCBF and $P_{br}O_2$ for all 23 studies as well as for the 15 patients during the first SPECT and the 8 patients during the second SPECT study separately. Though a weak tendency could be observed between low rCBF values and low $P_{br}O_2$ values (figure 4).

6.4 Discussion

Measurement of $P_{br}O_2$ with a microcatheter reflects the oxygen status of a very local area in the white matter. Till now several studies showed that this local measurement technique is associated with global features such as changes in mean Arterial Blood Pressure (mABP), Cerebral Perfusion Pressure (CPP), arterial PCO_2, and with patient outcome.[1,2,6,7,8] In these studies the PO_2 catheter is positioned

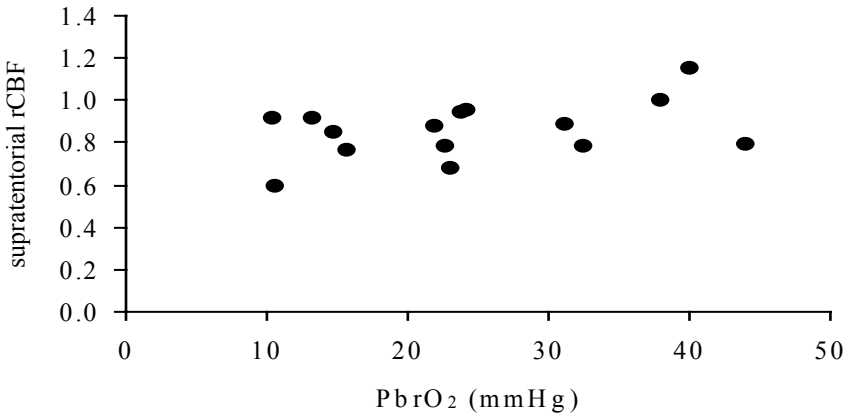

Figure 4. Graph showing the relationship between global supratentorial rCBF and the mean $P_{br}O_2$ of 1 hour before the first SPECT study. 15 studies were performed in this time period. Mean interval between time of injury and SPECT study was 18 ± 7 hours. No significant correlation could be found, though a slight tendency can be observed between low $P_{br}O_2$ and low rCBF values.

in a relative undamaged part of the frontal white matter. The conclusion is drawn that this local measurement method in a relative healthy part of the brain reflects the global oxygen status of the brain, though it is known that a marked heterogeneity exists in CBF. $P_{br}O_2$ measurement in this situation is aimed at preventing secondary ischemic insults in this relative healthy part of the brain. If the catheter is placed within a contusion or ischemic penumbra region a substantial lower $P_{br}O_2$ value will be found compared to the surrounding tissue.[12,13,14] Monitoring in these threatened areas will provide information about tissue that can possibly be saved by optimising CBF treatment, but will not provide any information about global CBF or oxygenation. The question rises whether one should aim at monitoring these local disturbances, monitoring global CBF/oxygenation or both. Positioning of the $P_{br}O_2$ catheter is in this perspective essential. In this study we have chosen to place the catheter in a relative undamaged area.

No substantial difference exists between the rCBF in the region of the catheter placement compared to the global supratentorial rCBF. This finding supports the hypothesis that the local $P_{br}O_2$ measurement reflects the global brain oxygenation if the catheter is placed in a relative undamaged part of the brain.

We used SPECT with 99m-Tc HMPAO to verify whether CBF in the unilateral frontal region is representative for the global supratentorial CBF in patients with a severe head injury. 99m-Tc HMPAO is a pure flow marker and should therefore reflect the oxygen offer to the brain. The method of analysis of the SPECT studies provides semi quantitative CBF values. Global infratentorial HMPAO uptake is used as a reference to express supratentorial CBF. In patients with a severe head

injury the infratentorial region is relatively spared for focal lesions [9,10,11] and therefore infratentorial HMPAO uptake is considered to be constant over time.
Taking into account that the unilateral frontal rCBF is representative for the global rCBF and the fact that the local $P_{br}O_2$ value is associated with outcome and therefore indicative for the global CBF, we expect that the frontal rCBF and the local $P_{br}O2$ are closely related to each other. Indeed both methods show the same time related tendency. Low values in the early posttraumatic phase stabilizing towards values beyond this period. During the first SPECT study, low global and frontal rCBF values were found compared to values found on day 6 and 14 after trauma. This time related tendency can be explained as a confirmation for the global character of the local $P_{br}O_2$ measurement, which shows the same time related tendency.
To the contrary in 5 patients with a focal lesion visible on CT and SPECT scanning within the frontal lobe in which the $P_{br}O_2$ catheter is placed no low rCBF values were found. Only in one patient with a lesion on CT a low frontal rCBF in combination with a very low $P_{br}O_2$ was found. In this patient a large contusion on CT scan was seen in the catheter measurement area. Possibly the automatic method of analysis of the SPECT studies is to rough to represent the very local $P_{br}O_2$ value. The frontal region, ipsilateral to the $P_{br}O_2$ catheter, that was chosen as a region of interest constitutes of 40% of the total volume of the hemisphere. Intracranial lesions which compromise a major part of this frontal region are seldom. In most cases frontal contusions compromise just the basic part of this region of interest, while $P_{br}O_2$ measurements were localised in the superior part of the frontal region. Heterogeneity in the large frontal region is missed during calculation of rCBF in predefined ROI's. Only in case of a large contusion that fills a substantial part of the frontal ROI a low $P_{br}O_2$ will be found. To the contrary if the contusion is only a part of the CBF region no low $P_{br}O_2$ values are found. This probably provides an explanation for the moderate correlation between calculated rCBF and $P_{br}O_2$.
SPECT studies are more sensitive for disturbances in CBF and show often larger deficits than CT studies [9,15,16,17]. In comparing early SPECT and CT studies one would expect to find more lesions in the SPECT studies. In this group of patients, in the early phase after trauma, no lesion that was seen with SPECT in the frontal area was missed with CT, to the contrary more lesions were detected with CT scanning. Even for the whole supratentorial region, CT scanning showed more lesions than SPECT, though both methods showed lesions which were not seen with the other study type. Early posttraumatic disturbances in CBF are probably due to structural/anatomical damage that is well detected with CT scanning. Positioning of the $P_{br}O_2$ catheter in a relative undamaged area is therefore adequately performed with CT scanning alone in the acute stage after trauma.
Late changes in CBF that are more likely due to non structural damage, for example secondary insults, do not result immediately in anatomical changes. CT scanning therefore can miss these changes, while SPECT studies will detect these changes more easily. In one patient we found a late macroscopical CBF lesion in the frontal region without anatomical substrate on CT scan. In three other patients late disturbances in macroscopical CBF in other parts of the supratentorial region we observed, without a visible lesion on CT scanning. In all but one of these patients

low initial $P_{br}O_2$ values indicative for global ischemia were present. The patient with the late lesion in the frontal region, had initial low $P_{br}O_2$ values and developed late low $P_{br}O_2$ values. In this situation the late low $P_{br}O_2$ value is representative for local ischemia, and not any more for global brain oxygenation.
In this study only a weak association between the absolute $P_{br}O_2$ and the local or global rCBF is found. Other explanations than the already given can be sought within the limitations of this study.
Measuring $P_{br}O_2$ reflects the balance between oxygen offer and demand. In SPECT with HMPAO only CBF is represented. CBF is one of the determinants in oxygen offer. Oxygen content of the blood is not represented with this method. Besides SPECT studies do not provide any information about the oxygen demand of the brain tissue. On the other hand, adequate CBF is essential for normal brain metabolism and therefore an association between $P_{br}O_2$ measurement and CBF measurement with SPECT would be expected. Other studies that compared $P_{br}O_2$ measurements with CBF studies found a more pronounced relationship between these two methods.[7,18] In these studies Xenon CT scanning was used to determine CBF. Xenon CT scanning gives in contrast to SPECT absolute CBF values. Besides spatial resolution and image fusion are more accurate in Xenon CT scanning than in the SPECT method we used. This may be an explanation for the better association between $P_{br}O_2$ values and CBF in these studies.
Another explanation for the weak association between $P_{br}O_2$ and rCBF could be sought in case of shunting. In this situation a high CBF will result in a high HMPAO uptake without a high tissue $P_{br}O_2$, because shunting vessels do not contribute to tissue oxygenation. Measuring $P_{br}O_2$ is a real time method, which gives an absolute value. Measuring rCBF with SPECT reflects the distribution of blood flow during the moment of injection of the tracer. During transport and data acquisition for the SPECT study, no brain tissue PO_2 could be measured. During transport secondary insults occur.[19] To compensate for possible changes in CBF just prior to the SPECT study mean $P_{br}O_2$ during the hour before data acquisition was used for analysis, but still this value is a reflection of the actual situation after transport.
Another point of interest is the spatial resolution of the SPECT study. Spatial resolution of the method that in this study is used is about $1cm^3$. No structural damage was visible on CT and no functional damage on SPECT round the $P_{br}O_2$ catheter tip in all but 2 patients, but given the known spatial resolution very small changes in CBF are missed. Besides the exact position of the $P_{br}O_2$ catheter could not be localised in the SPECT study. Regional instead of local CBF values are obtained. Probably a method with optimal image fusion possibilities and higher spatial resolution such as Xenon CT scanning [7,18] will result in a better association between local CBF and $P_{br}O_2$ values.
The underlying SPECT method is only capable to give relative CBF values. Using the infratentorial CBF as a standard for supratentorial CBF one assumes that infratentorial CBF is without disturbances and constant over time. In the underlying patient group no structural damage in the infratentorial region could be observed on CT scanning, but it is obvious that in a small portion of head injured patients there will be structural infratentorial damage [11] and thus CBF lesions. Besides in case

of large supratentorial lesions, infratentorial CBF can be disturbed by diaschisis. Both mentioned circumstances cause an overestimation of supratentorial rCBF.

6.5 Conclusion

The relatively undamaged frontal region in patients with a severe head injury is representative for the global supratentorial CBF, measured by means of SPECT. Cerebral damage in the acute phase after trauma is adequately diagnosed by means of CT scanning. Positioning of a $P_{br}O_2$ catheter is reliable with only CT-scanning. CT scanning can miss late changes in CBF. The relationship between $P_{br}O_2$ and regional or global rCBF is weak, possibly due to technical deficiencies in the measurement of rCBF by SPECT and lack of spatial resolution or an essential difference in measured qualities.

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CHAPTER 7

Serial Transcranial Doppler measurements in Traumatic Brain Injury with special focus on the early posttraumatic period.

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Acta Neurochirurgica 144: 1141-1149,2002

Abstract

*Background:*Cerebral ischemia is considered a key factor in the development of secondary damage after Traumatic Brain Injury (TBI). Studies on Cerebral Blood Flow (CBF) have documented decreased flow in over 50% of patients with TBI, studied in the acute phase. Transcranial Doppler (TCD) sonography is a non-invasive technique, permitting frequent or continuous measurements of blood flow velocity in the basal cerebral arteries.

*Objectives:*To investigate the potential of TCD to detect decreased blood flow velocity in the early phase after TBI;
To investigate whether flow velocity differs between hemispheres in patients with focal lesions versus those with more diffuse injuries;
To investigate if decreased blood flow velocity is indicative of cerebral ischemia, as evidenced by measurements of brain tissue PO_2.

*Methods:*TCD examinations were performed in 57 patients with severe TBI (GCS ≤ 8) daily over a period of 10 days. In 24 patients attention was focussed on the acute phase, performing measurements three times in the first 24 hours after injury and twice during the second day. A low flow velocity state (LFVS) was defined as a flow velocity ≤ 35 cm/sec in one or both MCA's within 72 hours after trauma. $P_{br}O_2$ was measured in 33 patients with an intraparenchymal Clark type electrode (Licox).
Patients were differentiated into those with primarily unilateral pathology on the admission CT scan versus those with primarily more diffuse or bilateral pathology. Outcome was evaluated at six months after injury, according to the Glasgow Outcome Scale (GOS).

*Results:*A low flow velocity state was observed in 63% of patients studied. Decreased flow was most pronounced during the first eight hours after injury and was accompanied by high pulsatility indices, especially at the side of the lesion. Flow velocity increased significantly after this time period. Initial Vmca values had a strong correlation with ipsilateral measured $P_{br}O_2$ values ($R = 0.73$). The occurrence of a LFVS was associated with poorer outcome (odds ratio 3.9).

*Conclusions:*TCD studies show reduction of cerebral blood flow velocity in the acute phase after traumatic brain injury. Decreased flow velocity is most pronounced ipsilateral to focal pathology. A low flow velocity state is probably due to high peripheral resistance, and is indicative of ischemia, as demonstrated by the association with decreased $P_{br}O_2$. A low flow velocity state is of prognostic value and identifies patients at increased risk for ischemia. Early TCD studies are recommended in TBI.

Keywords: Traumatic Brain Injury, Transcranial Doppler Sonography, Prognosis, Outcome, Brain tissue PO_2.

7.1 Introduction

Doppler technology for assessing blood flow velocity in intracranial arteries was first used by Aaslid et al. in 1982.[1] Clinical interest has mainly focussed on examinations of the Middle Cerebral Artery (MCA) and the Internal Carotid Artery (ICA). Technical aspects and normal values have been described.[1,20] Blood flow velocity is correlated to the diameter of insonated vessels [2] and changes in blood flow velocity to changes in cerebral blood flow.[3] In subarachnoid hemorrhage increased flow velocity and an increased MCA / ICA ratio are indicative of vasospasm.[13,14,21,25] Consequently the primary reason for conducting TCD studies in patients with SAH is detection of vasospasm.
Also in the field of TBI, TCD studies have focussed on the detection of vasospasm, prompted by the frequent occurrence of traumatic subarachnoid hemorrhage and its association with poorer outcome. Several TCD studies [9,11,12,16,24,26,27,28] have shown that mean flow velocity in the MCA (Vmca) increases after trauma, reaching a maximum at five days after injury.
Surprisingly, few studies have concentrated on the initial 24 hours after injury [18,22], a period during which low cerebral blood flow (CBF) and ischemia occur frequently. CBF studies utilizing radioactive Xenon or stable Xenon techniques have shown decreased CBF, particularly during the first eight hours after injury.[4,5] We have further shown low oxygen tension values in brain tissue to occur in over 50% of patients with severe TBI. Depth and duration of low values was associated with poorer outcome.[6,23]
TCD studies may be considered an appropriate diagnostic aid for detecting low flow velocities in the early phase after trauma, and, because of their easy bedside availability, repeated measurements may be performed. Detecting ischemia at an early stage can provide opportunities for therapeutic intervention. The aim of this study is to evaluate the time course of flow velocity in the MCA after TBI, to investigate whether flow velocity differs between hemispheres in patients with focal lesions, versus those with more diffuse injuries and to investigate whether decreased flow velocity is indicative of cerebral ischemia, as evidenced by measurements of brain tissue PO_2.

7.2 Material and methods

Patient population

Fifty-seven patients (48 men and 9 women) with a severe non-penetrating TBI (Glasgow Coma Scale ≤ 8) were prospectively investigated. The research protocol was approved by the institutional review board and informed consent was obtained from relatives of all participating patients. Characteristics of the cohort are described in table 1. All patients were admitted to the Neuro-intensive care unit and treated according to a standard protocol, conforming to the principles described in the European Brain Injury Consortium guidelines.[15] This included rapid detection

and evacuation of intracranial mass lesions, treatment of sustained raised Intracranial

Table 1. Patient characteristics.

number of patients		57
male		48 (84%)
mean age ± std		33 ± 18
mean GCS ± std		6.1 ± 1.6
GOS	Dead	15 (26%)
	Vegetative	3 (5%)
	Severely disabled	14 (25%)
	Unfavorable	56%
	Moderately disabled	12 (21%)
	Good recovery	11 (19%)
	Favorable	40%
	Unknown	2 (4%)
CT classification		
tSAH		39 (68%)
TCD classification		
LFVS		36 (63%)
HFVS		10 (18%)
Lindegaard index > 3*		14 (25%)
$P_{br}O_2$ available		33 (58%)

* 2 unknown

Pressure (ICP) and maintenance of adequate Cerebral Perfusion Pressure (CPP). Outcome was assessed six months after injury according to the 5-point Glasgow Outcome Scale (GOS).

Monitoring

Invasive mean arterial blood pressure (mABP), ICP, CPP (=mABP-ICP), arterial oxygen saturation (SaO_2), end-tidal CO_2 and $P_{br}O_2$ were continuously monitored. ICP was monitored with a fiberoptic device (Camino Laboratories, San Diego, USA). $P_{br}O_2$ was monitored with a Clark type electrode (Licox, GMS, Germany) positioned in the frontal white matter. ICP and $P_{br}O_2$ catheters were introduced through a modified intracranial bolt in an undamaged part of the frontal lobe, preferably on the right side. ICP and $P_{br}O_2$ monitoring were initiated as soon as possible in the intensive care unit, with an intended duration of at least five days.
Transcranial Doppler (TC 2-64 and TC 2020, Eden Medical Electronics, Kent, Washington, USA) measurements of both MCA and extracranial ICA were performed as soon as logistically possible after trauma, and subsequently daily until 10 days after trauma. Twenty-four patients were measured three times during the first 24 hours and twice during the second 24 hours after trauma. TCD measurements were performed by two of the authors (HvS and JWS) with one observer studying each individual patient. The MCA was insonated through the

temporal window and the ICA in the upper cervical region. The depth of insonation giving the highest value was chosen for measurements at each side. Mean flow velocity of the MCA (mVmca) and the ICA (mVica) were measured, the Pulsatility Index calculated and the ratio in velocities (Lindegaard Index) [14] between the two arteries (MCA / ICA), was calculated. A low flow velocity state (LFVS) was defined as a clearly reduced flow velocity ≤ 35 cm/sec (below the range of normal values) in one or both MCA's within 72 hours after injury. A high flow velocity state (HFVS) was defined as a Vmca > 100 cm/sec in one or both MCA's during at least two subsequent measurements. Simultaneous to TCD-studies all monitored parameters were recorded. Patients were differentiated according to the admission CT-examination into those with:

- primarily unilateral pathology, as defined as shift ≥ 2 mm or unilateral focal intraparenchymal damage, and
- those with primarily diffuse or bilateral pathology as defined by the absence of shift and/or absence of focal lesions.
- Relatively low numbers precluded further differentiation between patients with diffuse or bilateral pathology.

In patients with primarily unilateral pathology TCD values were differentiated between the "lesion" (L) and a "non-lesion" (NL) side. In the absence of unilateral pathology no statistical differences were noted between the right and left side and results are therefore reported as the mean value for both sides.

Statistics

For analysis a T-test or a Mann Whitney U test was used. For binomial values a Chi-square-test was used. The prognostic value of a LFVS was determined by correlating outcome with the main clinical and CT- variables in a linear logistic regression model (SPSS software, V.9, SPSS Inc., Chicago Ill USA). P-values ≤ 0.05 were considered statistically significant.

7.3 Results

Thirty-six patients were categorized in the group with primarily unilateral pathology and 21 patients in the group with primarily diffuse or bilateral pathology. Figures 1 and 2 show the time course of mean MCA velocity and mean ICA velocity in both groups, presenting the data obtained at the lesion and non lesion side in patients with focal pathology and averaged values of both sides for patients with diffuse or bilateral pathology. Detailed results differentiating mean values on the lesion side and non-lesion side in patients with focal pathology and average values for patients with diffuse or bilateral pathology for the MCA flow velocity are presented in table 2, including information on Pulsatility Index (PI) and Cerebral Perfusion Pressure (CPP.) The lowest recorded flow velocities were observed in the first eight hours after trauma, with a mean Vmca at the side of the lesion in patients with focal pathology of 33.6 ± 16.9 cm/sec, significantly lower than reported normal values (43-67 cm/sec). During the first 36 to 72 hours after injury mean

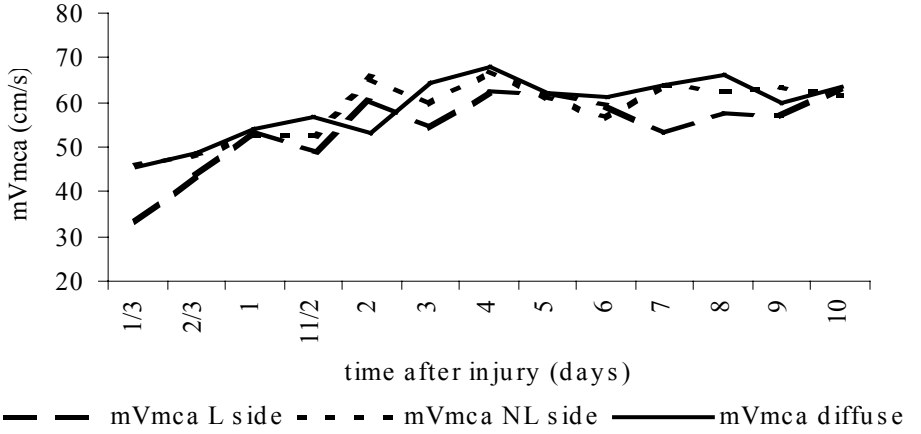

Figure 1. Graph showing the mean flow velocity values according to the time after injury in the middle cerebral artery, presenting results obtained at the lesion and non-lesion side in patients with unilateral pathology and averaged values from both sides for patients with diffuse or bilateral pathology.

Vmca increased to normal values, both in patients with unilateral and were measured on diffuse pathology. This increase in Vmca was statistically significant, but most prominent in patients with focal pathology on the lesion side (P=0.01, T-test) and in patients with diffuse pathology (P=0.003, T-test). Highest mean values

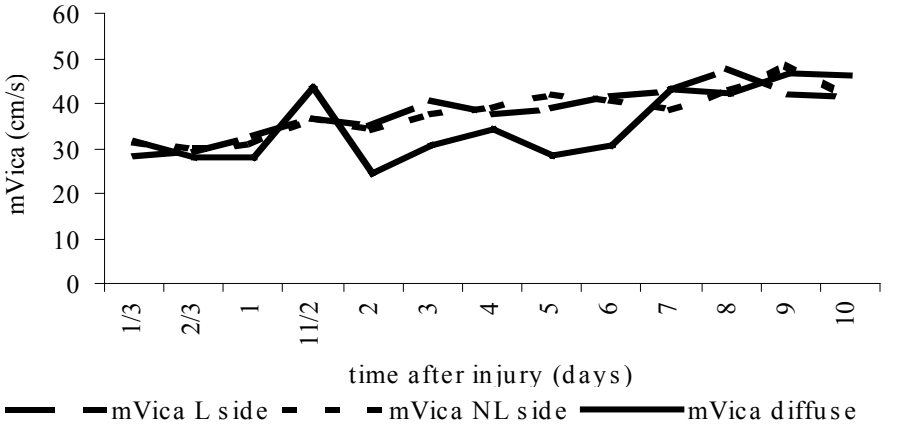

Figure 2. Graph showing the mean flow velocity values according to the time after injury in the internal carotid artery, presenting results obtained at the lesion and non-lesion side in patients with unilateral pathology and averaged values from both sides for patients with diffuse or bilateral pathology.

Table 2. Time course of blood flow velocity, pulsatility index and CPP in TBI.

		Unilateral Pathology					Diffuse or bilateral pathology			
		Lesion side		Non Lesion side						
time after injury days/hrs.	No. pat.	Vmca (cm/s)	PI	Vmca	PI	CPP (mmHg)	No. pat.	Vmca (mmHg)	PI	CPP
Day 1										
0 – 8	22	33.6*	2.1	46. 1*	1.7	74	16	45.3	1.6	75
9 – 16	23	43.8	1.3	48.2	1.3	74	12	48.8	1.2	79
17 – 24	24	53.8	1.1	52.8	1.3	79	12	54.2	1.0	80
Day 2										
25 – 36	32	49.1	1.5	52.5	1.4	80	19	56.8	1.0	81
37 – 48	15	60.5	1.0	65.1	1.1	72	12	53.2	1.0	82
Day 3	28	54.3	1.1	59.7	1.5	80	17	64.2	0.9	86
Day 4	26	62.4	1.3	67.2	1.3	81	19	67.9	0.9	82
Day 5	27	62.3	1.2	61.1	1.3	77	16	62.3	0.9	86
Day 6	24	59.3	1.3	56.6	1.5	78	15	61.2	1.1	88
Day 7	25	53.2	1.3	64.1	1.2	83	12	63.8	1.2	72
Day 8	22	57.5	1.4	62.6	1.3	74	9	66.2	1.0	83
Day 9	23	57.3	1.2	63.6	1.2	80	10	59.9	1.1	75
Day 10	16	63.3	1.1	61.6	1.2	79	7	63.6	0.9	

Mean flow velocities in the middle cerebral artery (Vmca),pulsatility indexes and CPP in patients with unilateral (differentiated into lesion and non-lesion side, and in patients with diffuse or bilateral pathology (mean of both sides) at different time periods after injury. *) P=0.02, paired T-test.

of Vmca day 3 after injury, but did not exceed normal values. In individual patients, however, a broad spectrum of Vmca was found. The highest measured value observed in one patient was 170 cm/sec on day 7 post injury. Initial low mean Vmca values were accompanied with high mean PImca values, especially on the lesion side in patients with focal pathology. As Vmca values increased, PImca decreased. This decrease in mean PImca was statistically significant on the side of the lesion in patients with unilateral pathology (P=0.03, T-test) and in patients with diffuse or bilateral pathology (P=0.01, T-test) (figure 3, table 2).

Unilateral versus diffuse pathology

In patients with unilateral pathology mean Vmca at the lesion side was significantly lower during the first eight hours after injury compared to the non-lesion side (P=0.02; paired T-test). Differences were also significant in comparison to the mean Vmca in patients with diffuse or bilateral pathology (P=0.04). These initial low Vmca-values were associated with high ipsilateral PImca values, although differences in calculated PImca between groups were not significant (table 2).
After day 1 mean Vmca values were comparable between patients with unilateral and diffuse pathology and differences between lesion and non-lesion side in patients with unilateral pathology disappeared.

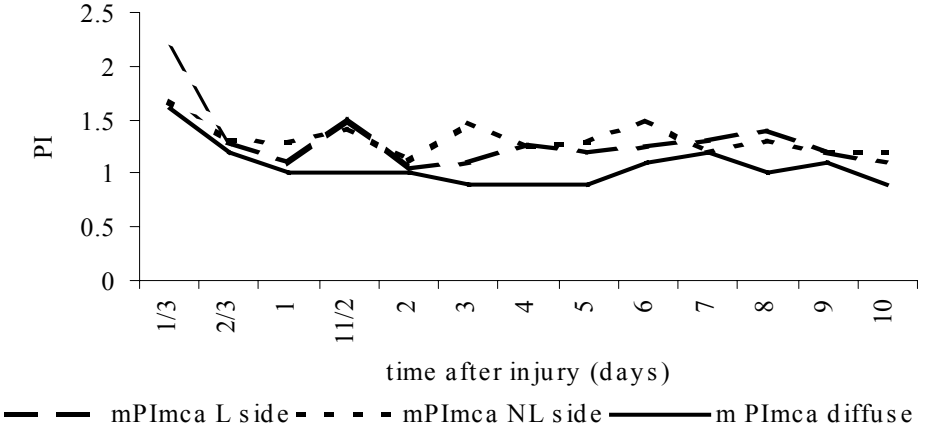

Figure 3. Graph showing the mean pulsatility index values according to the time after injury in the middle cerebral artery, presenting results obtained at the lesion and non-lesion side in patients with unilateral pathology and averaged values from both sides for patients with diffuse or bilateral pathology.

Low flow velocity state

In 36 out of 57 (63%) patients a LFVS was observed. This occurred more frequently in patients with unilateral pathology (78%) than in patients with diffuse or bilateral pathology (38%). Differences in occurrence of LFVS between these two groups was statistically significant (P=0.003, Chi-square test). In patients with unilateral pathology (N=36) a bilateral LFVS was observed in 13 cases, a unilateral LFVS at the lesion side in 12 cases and at the non-lesion side in three cases.
A statistically significant relation was found between the occurrence of a LFVS and the severity of injury, age, occurrence of traumatic subarachnoid hemorrhage (tSAH), the degree of midline shift, CT-classification and outcome. Mean GCS of patients with LFVS was 5.6 ± 1.7 and in patients without a LFVS 6.9 ± 1.1 (P=0.008, Mann Whitney U test). The age in patients with a LFVS was higher compared to patients without LFVS (38 ± 18 years versus 27 ± 5 years; P=0.03 Mann Whitney U test). Patients with a LFVS had a significantly higher incidence of tSAH than patients without LFVS (P=0.05, Chi-square test, table 3). Mean midline shift in patients with LFVS was 4.9 ± 5.7 mm versus 1.71 ± 3.26 mm in patients without LFVS (P=0.01, Mann Whitney U test). A strong correlation was noted between LFVS and unfavorable outcome (P=0.01, Chi-square, table 4). Univariate analysis showed a strong association between LFVS and death (odds ratio 4.8; CI:

0.96-24) and between LFVS and unfavorable outcome (odds ratio 3.9; CI: 1.2-13). If covariate adjustment was performed for initial GCS, age, the occurrence of tSAH

Table 3. Traumatic subarachnoid hemorrhage and low flow velocity state.

tSAH	Low Flow Velocity State		
	Yes	No	Total
Present	28	11	39
Absent	8	10	18
Total	36	21	57

Association between tSAH on admission CT and Low Flow Velocity State (within 24 hours of injury). P=0.046, Chi-square test.

and CT classification the predictive value of a LFVS decreased substantially (table 5), with the initial GCS appearing as strongest covariate.

Table 4. Low flow velocity state and outcome.

Outcome	Low Flow Velocity State		
	Yes	No	Total
Unfavorable	25	7	32
Favorable	11	12	23
Total	36	19	55 *

Unfavorable outcome is more frequent in patients with a LFVS (P=0.012, Chi-square test). *) Outcome unknown in 2 patients.

High flow velocity state

A high flow velocity state (HFVS), defined as Vmca > 100 cm/sec, was observed less frequently than a LFVS occurring in only ten out of the 57 patients studied. In eight patients flow velocity increased to over 120/sec. A HFVS was never seen during the first 16 hours after trauma, and started on average during day 2 and 3 postinjury. In two patients a late onset of HFVS on day 6 and 8 after injury was seen, possibly indicative of vasospasm. HFVS was predominantly seen in patients with unilateral pathology (n = 8) and was noted only twice in patients with diffuse or bilateral injuries.

No statistically significant association could be found between the occurrence of HFVS and initial GCS, age, CT-classification, tSAH and outcome six months after injury. The presence of midline shift on the admission CT scan was more pronounced in patients with HFVS (6.5 ± 5.7 mm) compared to patients without HFVS (3.11 ± 4.7 mm), but differences were not significant (P=0.14, T test).

Lindegaard Index

In patients with unilateral pathology no significant changes were noted in the Lindegaard Index. In patients with diffuse or bilateral pathology mean Lindegaard Index increased significantly up till day 3, reaching mean values of 2.2 (P=0.01, T-test).

Table 5. Prognostic value of a Low Flow Velocity State (LFVS).

	Outcome 6 months after injury	
	Unfav./Fav. Odds ratio (95% CI)	Dead/Alive Odds ratio (95% CI)
LFVS	3.9 (1.2-13)	4.8 (0.96-24)
Corrected for: GCS, age, tSAH and CT classification	1.2 (0.25-5.9)	2.1 (0.33-14)

Odds ratios and 95% Confidence Intervals (95% CI) in analysis of prognostic value of a LFVS versus outcome 6 months after injury for.

In 14 out of 55 patients a Lindegaard Index > 3 during two subsequent measurements or once bilaterally was observed: in nine patients with unilateral pathology and in five with diffuse or bilateral pathology. In patients with unilateral pathology the Lindegaard Index was above 3 bilaterally in four out of nine patients. A strong association was noted between an increased Lindegaard Index and the occurrence of HFVS (P=0.006, Chi square test, table 6). No statistically significant association was observed between an increased Lindegaard Index and GCS, age, shift, tSAH, CT-classification and/or outcome.

Table 6. Lindegaard Index and high flow velocity state.

LI >3	High Flow Velocity State		
	Yes	No	Total
Present	6	8	14
Absent	4	37	41
Total	10	45	55*

Association between a Lindegaard Index >3 and High Flow Velocity State (P=0.006, Chi-square test).
*) Two patients with unknown LI .

TCD and $P_{br}O_2$

A strong correlation was observed between Vmca and $P_{br}O_2$ values measured within eight hours after injury, ipsilateral to the $P_{br}O_2$ probe in patients with unilateral pathology, as well as to the mean Vmca in patients with diffuse pathology (R = 0.73, figure 4). No correlation was found between initial $P_{br}O_2$ values and the Vmca

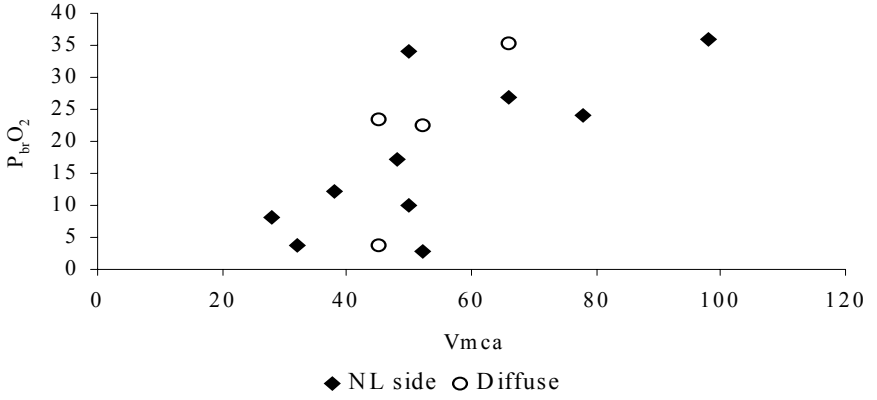

Figure 4. Graph showing the relation between flow velocity values in the middle cerebral artery obtained ipsilateral to the $P_{br}O_2$ sensor and the simultaneously measured brain tissue PO_2 values ($P_{br}O_2$). R=0.73.

on the lesion side in patients with unilateral pathology, generally contralateral to the $P_{br}O_2$ probe. Beyond the initial eight hours after injury no linear correlation could be observed between flow velocity values and $P_{br}O_2$. No differences in mean $P_{br}O_2$ during the whole period of observation were detected between patients with or without a LFVS or HFVS. A tendency for association between initial low Vmca values and initial low $P_{br}O_2$ values (≤ 10 mmHg during at least 30 minutes, within the first 24 hours after trauma) was noted, but differences were not statistically significant. No correlation was seen between initial low $P_{br}O_2$ values, and a HFVS or increased Lindegaard Index.

7.4 Discussion

Ischemic insults after severe TBI occur frequently and are correlated to poorer outcome.[4,5,7] Measurements of CBF permit detection of such episodes, but are complex, expensive or do not permit continuous monitoring. In contrast, TCD measurements are simple, non-invasive, relatively cheap and can either be performed repeatedly or on a continuous basis. TCD measurements however do not measure actual blood flow, but flow velocity through the basal cranial arteries. Bishop et al. [3] and Shigemori et al. [27] showed that changes in flow velocity in the MCA correlated well with changes in hemispherical CBF. However, the relation is variable and dependent on the diameter of basal cerebral arteries. In vasospasm for instance blood flow velocities are increased due to the constriction of vessels, whilst actual CBF is decreased. In our studies we particularly concentrated on a low flow velocity state occurring in the acute phase after TBI. A low flow velocity can be due to low CBF secondary to low cardiac output, to larger diameter of the insonated vessel or due to a high peripheral resistance or combination of these

factors. Theoretically TCD measurements may discriminate between these situations. If low flow velocity in the MCA results from low cardiac output, the ratio in flow velocity between MCA and ICA will be normal and the Pulsatility Index (PI) in both vessels is also normal. In case of a large diameter of the MCA, ICA flow velocity may be expected to be relatively high in combination with a low PI in the MCA. If the cause of low flow velocity is a high peripheral resistance the PI in both MCA and ICA vessels will be increased and the MCA/ICA ratio remains normal or low. Martin et al. [17] reporting on results of a prospective study in 125 patients of cerebral blood flow (measured using 133 Xenon clearance), transcranial Doppler measurements, measurements of cerebral arteriovenous oxygen difference and cerebral metabolic rate of oxygen differentiated three phases of CBF after TBI: phase I is characterized by hypoperfusion occurring on the day of injury, phase II is characterized by hyperemia with increased CBF and phase III is the vasospasm phase, occurring between days 4 and 15. Somewhat surprisingly Martin et al. [17] do not describe a decreased flow velocity on transcranial Doppler studies, performed during the hypoperfusion phase on day 1. However, only 42 of the 125 patients were studied within the first day after injury and no mention is made of the number of hours after injury, at which studies were performed. In the present series we specifically paid attention to the early posttraumatic phase. We documented a low flow velocity in the MCA, most pronounced during the first eight hours after injury and significantly lower on the lesion side, as compared to non-lesion side, or to patients with more diffuse injuries. The low flow velocities were accompanied by an increase in Pulsatility Index, suggestive of a high peripheral resistance. These findings are consistent with the study reported by Muizelaar et al. [19], showing a prolonged transit time in a cohort study of 71 patients, using rapid sequence CT scanning after a bolus infusion of contrast, suggestive of an increase in cerebral vascular resistance, due to narrowing of the microcirculation. In a study on CO_2 reactivity and brain tissue oxygen tension we found a very low or absent influence of reducing P_aCO_2 on $P_{br}O_2$ during the first 24 hours after injury and it was considered likely that this absence was caused by a generalized state of vascular narrowing.[8] Therefore accumulating evidence exists that a LFVS and ischemia is a particular risk within the first 24 hours after injury and that this is caused by a high peripheral resistance, which may be secondary to microcirculatory disturbance and/or mitochondrial dysfunction. A better understanding of the cause of a LFVS may permit more appropriate targeting of therapy to patients with TBI. If the cause is primarily a microcirculatory disturbance vasopressors may be considered to elevate CPP, consequently improving CBF. Conversely, hyperventilation may be contra-indicated in patients with a LFVS, as it may further increase peripheral resistance. If mitochondrial dysfunction is the main problem, CPP therapy may not have any benefit. We propose that TCD examinations during the first 24 hours after injury should be more routinely used in order to permit rapid detection of impending ischemia, providing a therapeutic window, even before the patient is admitted to the neurosurgical intensive care unit.

After the initial 24 hours average flow velocity in the MCA increased, reaching a maximum on day 3 and 4. A HFVS was seen in 10 patients, with maximum values up to 170 cm/sec in individual patients on day 3 and 4. These findings are

consistent with the hyperemia phase, described by Martin et al. [17] and with other reports.[11,28] A HFVS may be due to hyperemia or vasospasm. In hyperemia a low Pulsatility Index may be expected and the MCA/ICA-ratio will be normal or low. Criteria for TCD diagnosis of vasospasm have been described in spontaneous subarachnoid hemorrhage. A flow velocity above 100 cm/sec indicates moderate and above 200 cm/sec severe spasm. Lindegaard introduced the MCA/ICA-ratio and considered a ratio > 3 indicative of vasospasm. It is however questionable whether these criteria may be applied uncritically in patients with TBI. The incidence of vasospasm in TBI varies in different reports from 5 to 57%.[11,12,16,28,29] In the current series increased flow velocity of the MCA was found in only 10 patients and an increased Lindegaard Index in 14. Full criteria for vasospasm as evidenced by an increase of flow velocity above 100 cm/sec and an increased Lindegaard Index was only demonstrated in six patients, considerably fewer than in the series reported by Martin et al. .[17] There was further some discordance between the two spasm parameters. Already within 16 hours after injury an increased Lindegaard ratio was found in six patients. In these patients the MCA flow velocity was normal, but flow velocity in the ICA decreased. Whether this signifies a decreased flow through the MCA in combination with narrowing of the MCA-segment remains debatable.

Previous reports have shown an increased incidence of posttraumatic vasospasm in patients with traumatic subarachnoid hemorrhage.[16,25,28] In our study tSAH was visible on the admission CT scan in 39 patients. We however found no positive association between the presence of tSAH and increased flow velocity in the MCA and/or increased Lindegaard Index. The interrelation between flow velocity, vascular diameter and metabolic flow requirements are complex. PET-studies have demonstrated a suppression of cerebral metabolic rate beyond the first four to five days after injury. Even with additional monitoring of cerebral oxygenation differentiation may be difficult.

We found a strong linear association between Vmca and $P_{br}O_2$ in the relatively undamaged part of the brain during the first eight hours after injury, indicating that flow velocity and cerebral oxygenation are strongly related during this period. These findings are consistent with observations by Dings et al. [10], describing a reduction in flow velocity concurrent with a reduction in $P_{br}O_2$ after induced hypocapnia. However, the relation between a LFVS and initial low $P_{br}O_2$ values was only weak. A possible explanation for this apparent discrepancy is that in monitoring brain tissue oxygen measurements were performed on the side contralateral to the lesion, e.g. in a relatively undamaged part of the brain. In almost 50% of the patients with a LFVS the low flow velocity values were only registered ipsilateral to the lesion, thus contralateral to the brain oxygen sensor. Furthermore, the time windows for defining a LFVS and initial low $P_{br}O_2$ values were different. A LFVS was defined as one or more clearly reduced flow velocity values during 72 hours after injury, while initial low $P_{br}O_2$ values were measured within the first 24 hours after injury. The influence of the different time window definitions however may be presumed to be small, as a LFVS predominantly occurred also within the first 24 hours. We therefore presume that the lower Vmca values measured during a LFVS, are indicative for the CBF in the damaged part of the brain, while the low

$P_{br}O_2$ values, measured in a relatively undamaged region, are more indicative of global cerebral oxygenation. Our intention in monitoring $P_{br}O_2$ on the non-lesion side was primarily to be able to detect more global secondary insults to the brain. The findings of the TCD studies, demonstrating a significantly increased number of patients with a LFVS on the lesion side, would however more favor monitoring in the penumbra of the lesion side.

7.5 Conclusions

We conclude that TCD monitoring in TBI yields important information on cerebral blood flow velocity in a simple non-invasive way during the very early period after TBI and should be more routinely performed in these patients. A LFVS is frequent within the first eight hours after injury, particularly ipsilateral in the presence of focal pathology. Low flow velocity values are accompanied with a high Pulsatility Index, indicating low CBF to be due to high peripheral vascular resistance. TCD values are related to the ipsilateral $P_{br}O_2$ values during the first eight hours after injury and may possibly detect patients who are at increased risk for ischemia, thus permitting more targeted therapy.

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CHAPTER 8

General discussion

H van Santbrink

8.1 Introduction

For several decades investigators have tried to resolve the pathophysiological problem of secondary deterioration in patients with severe Traumatic Brain Injury (TBI). It is generally accepted that ischemia is one of the key factors which leads to secondary damage. Most parameters monitored are therefore directly or indirectly associated with Cerebral Blood Flow (CBF). As yet none of the parameters clinically monitored, continuously measures on-line oxygen metabolism directly in the affected organ, the brain. Jugular bulb oxymetry (SjO_2) can provide information on oxygen metabolism of the brain in an indirect way in the venous jugular blood if oxygen extraction is calculated. Microdialysis provides some information on oxygen metabolism, but has a time-lag and is still in the experimental phase of development.
Introduction of direct measurements of brain tissue PO_2 ($P_{br}O_2$) facilitated obtaining on-line information on oxygen metabolism in the affected organ. Following further technical improvements on stability of the micro catheter and on introduction and fixation techniques, and stimulated by promising results in the experimental setting, human measurements were initiated in patients with severe TBI.[1,2,3] Many questions arose from our preliminary work:

- What is the normal value of $P_{br}O_2$?
- Is it possible to get information about oxygen metabolism of the whole brain by a method that measures only in a very local area?
- Where should the catheter preferably be introduced? Relevant confounders are the marked heterogeneity existing in CBF, and whether the aim of monitoring is to obtain information in relatively undamaged parts of the brain or more specifically in the penumbra region surrounding focal lesions.
- Is the low values obtained initially real or an artifact?
- Which physiologic parameters influence $P_{br}O_2$?

In the underlying thesis we address these questions, adding information to our existing knowledge, but raising even more questions. In this chapter we will try to incorporate all the results of the different chapters in a single pathophysiologic synthesis.

8.2 Time course

Immediately after the impact to the brain, CBF is reduced dependant on the severity of the injury. Oxygen supply to the brain is reduced as CBF decreases and further compromised by secondary insults as hypoxia and hypotension (figure 1).
Experimental work shows $P_{br}O_2$ values between 25 – 35 mmHg [4,5] in sham operated animals, which probably approximate values under normal circumstances. The reduction in oxygen supply/CBF after injury is confirmed by the low $P_{br}O_2$ values observed in the initial phase after trauma (chapter 2,3). In our first paper, describing preliminary results in 22 patients, and in the subsequent report on the full 100 patients similar time related patterns of mean $P_{br}O_2$ are observed. Discussion developed whether these initial low values might be due to an artifact induced by

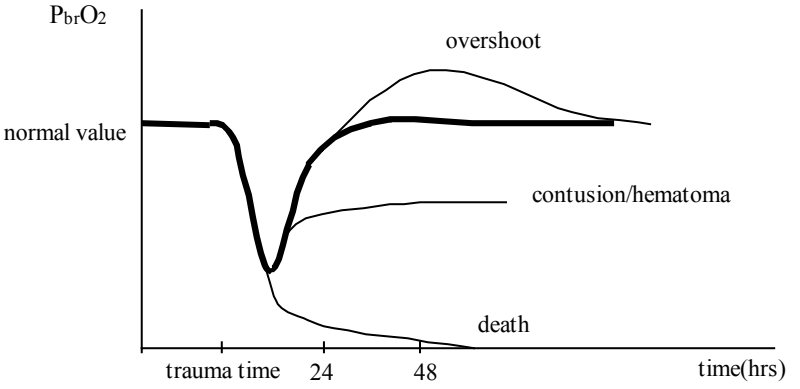

Figure 1. Hypothetical time course of $P_{br}O_2$.

local trauma after introduction of the microcatheter or reflect the actual situation correctly. We addressed this by analyzing the run-in time after introduction of a second catheter after several hours. This run-in time was at most 2 hours. Furthermore, animal studies conducted by our group showed only a very minimal zone of edema and/or a minimal blood accumulation around the microcatheter of insufficient volume to significantly influence measurements.[6] We concluded that our observation of initially low values of PbrO2 after TBI were a real pathophysiologic phenomen not caused by an artifact. However possible artifactual effects during the run-in time at which stabilization of the probe-tissue interface occurs following at most two hours after introduction could not be excluded and we decided to exclude data from the first 2 hours after introduction of the catheter from any of the analyses performed. Additional support for the hypothesis that initial low $P_{br}O_2$ values are due to a reduced CBF is provided by the results of simultaneous studies with SPECT and TCD.

In chapter 6 a positive correlation between regional relative CBF (rCBF) and ipsilateral $P_{br}O_2$ values is described during the first period after injury. Further evidence that the low initial $P_{br}O_2$ values are due to a reduced CBF is provided in chapter 7, showing a strong positive correlation between TCD flow velocity in the middle cerebral artery (Vmca) and ipsilateral $P_{br}O_2$ values during the first 8 hours after injury. The results described are in agreement with results of CBF studies performed with radioactive Xe or stable Xe-CT scanning in an early phase after trauma.[7,8]

Clinical evidence for the fact that the initial low $P_{br}O_2$ values are not due to an artifact is supported by the correlation found between depth and duration of initial low values and outcome six months after injury. During the first 24 hours after injury the occurrence of $P_{br}O_2$ values < 10 mmHg during a cumulative period of >

30 minutes is positively correlated with unfavorable outcome (odds ratio 3.8 for death and 2.8 for unfavorable outcome). The predictive value of these initial low values was found to be independent of clinical and CT parameters except for the obliteration of basal cisterns on the initial CT scan. SPECT studies showed that the rCBF in the frontal region ipsilateral to the catheter did not differ from the global supratentorial rCBF and produced additional evidence supporting the concept of measurements in a relatively undamaged part of the brain. We concluded that the local PbrO2 measured under these conditions may be considered representative for the global oxygenation of the brain during the initial period after injury.(chapter 6)
The decision to measure local $P_{br}O_2$ in a relatively undamaged part of the brain instead of the penumbra of a lesion or within the core of a lesion itself depends on the aim of $P_{br}O_2$ monitoring. Positoning the catheter in the penumbra zone of a lesion will provide information on the local situation and may be of importance when the primary aim is to rescue potentially viable tissue. We consider this a valid approach, but in our studies our primary intent was to obtain information on the more global status of brain oxygenation.
The mechanism, which is responsible for the decrease in $P_{br}O_2$ immediately after trauma remains unclear. Conceptually this may be caused by primary vascular effect, or by decrease in CBF secondary to decreased metabolism. Our findings that low Vmca values are accompanied by a high pulsitility index indicate a high peripheral resistance and provide support for the concept of vascular narrowing.(chapter 7) This may result from vasoconstriction of the arteriolae as direct effect of trauma, be secondary to metabolic depression, or due to compression of the microcirculation of the venous vascular bed caused by astrocytic swelling and clogging of the vessels with blood cells. Studies performed by Muizelaar et al.[9] with stable Xe CT techniques confirm this hypothesis. They found a reduced CBF in combination with a reduced Cerebral Blood Volume (CBV), during the first 24 hours after severe TBI. Since the venous side of the vascular bed mainly determines CBV, it can be concluded that the increased vascular resistance is caused by narrowing of the microvascular and venous bed, independent on the diameter of the largr regulating arteriolae. It may even be considered possible that the regulating arteriolae are (maximally) dilated as response to reduced CBF and impending ischemia. Moreover, astrocytic swelling may induce more marked narrowing of the venous vascular bed as this is more vulnarable to mechanic compression as compared to arteriolae with a more stiff muscular wall.
In conclusion we can consider it likely that a reduced CBF/oxygen supply to the brain, during the first period after TBI (24 hours), is probably caused by an increased vascular resistance at the microcirculatory or the venous level. Concurrently however reactive arterial dilatation may be present as response to impending ischemia.

8.3 Regulatory Mechanisms

Tissue Oxygen Response (TOR)

In this thesis O_2 and CO_2 regulatory mechanisms and their interaction were investigated in patients with a severe TBI.
In normal conditions O_2 regulatory mechanisms are active. A low oxygen offer will induce vasodilatation and increase CBF, and conversely a high oxygen offer will reduce CBF by means of O_2 sensitive regulatory arteriolae.[10] In chapter 4 the influence of an increased arterial PO_2 on $P_{br}O_2$ was investigated, and Tissue Oxygen Response (TOR) defined. During the first 24 hours after trauma patients with an unfavorable outcome showed to have a significantly higher TOR than patients with a favorable outcome. At this time period TOR was an independent predictor for unfavorable outcome with an odds ratio of 3.7. We presume that in cases of a severe head injury the O_2 sensitive arteriolae are incapable to react to changing P_aO_2 levels. Reactive arteriolar constriction/dilatation to keep tissue PO_2 between certain (normal) levels is impaired, resulting in an unlimited increase in tissue PO_2 levels in case of an increasing O_2 offer. The severity to which this mechanism is damaged correlates to the severity of the injury. We have to keep in mind that the incapability of the arteriolae to react on changing P_aO_2 levels does not provide any information on the diameter of these vessels, but only on responsitivity to changes in the balance between oxygen offer and demand. Since the oxygen demand/metabolism may be presumed constant during the short duration of the TOR test, the increased oxygen offer determines the changes in TOR.
If the oxygen demand/metabolism is impaired, a second mechanism that can result in a high TOR, is the incapability of the brain cell to metabolize the oxygen offer. Recent studies show that mitochondrial dysfunction occurs in the initial phase after trauma.[11] Patients with a more severe TBI are less capable to utilize the oxygen offered. This hypothesis assumes that the brain is relatively ischemic following injury. The additional oxygen that is offered to the brain will be metabolized in potentially salvageable brain tissue, but not in irreversible damaged brain tissue, resulting in respectively low and high TOR values.
Differentiation between these two mechanisms is not possible with the current data. Biochemical studies, such as microdialysis PET studies or monitoring with multi parametric catheters in the early phase after injury probably may provide additional information and clarification. The observation that simply increasing the FiO_2 (and subsequently P_aO_2) will decrease brain tissue lactate levels will decrease[12,13] is of great interest as it indicates that at least in some patients maintaining P_aO_2 at supra normal levels may improve oxygen metabolism, but the clinical relevance of such procedures for improving ultimate outcome remains to be proven.
The theories discussed do not explain why differences disappear after the initial period following injury. Neither the absolute level of $P_{br}O_2$, nor the TOR or CO_2 reactivity are related to outcome beyond this first 24 hours. These observations however do emphasize the importance of the first 24 hours after injury. The concept of the “first golden hour” in emergency medicine remains valid, but we feel that in

the intensive care treatment of patients with severe TBI the first 24 hours should be considered as " golden period".

CO_2 reactivity

CO_2 reactive mechanisms in the brain are responsible for a 3-4% reduction in CBF each torr reduction in P_aCO_2 in healthy persons, over the clinically important range of 20-60 mmHg.[14] The CO_2 regulating mechanisms are probably located in the smaller pial arteries. TCD studies show a correlation between disturbance in CO_2 reactivity and outcome.[15] In chapter 5 the influence of a decreasing P_aCO_2 on $P_{br}O_2$ is investigated. Increased hyperventilation causes a significant reduction in $P_{br}O_2$, most likely induced by vasoconstriction. During the initial period after trauma, CO_2 reactivity is absent or significantly reduced, indicating a reduced responsitivity of cerebral arteriolae to P_aCO_2 changes, which is in agreement with results found with TCD techniques[16] and with results found with $P_{br}O_2$ in other studies.[17] Again, the incapability of the regulating vessels to react to changes in P_aCO_2 does not provide any information about the diameter of these vessels. Based on the results from TCD studies, we had expected to find some relationship between $CO_2/P_{br}O_2$ reactivity and outcome but were unable to find any statistically significant results.

TOR and CO_2 reactivity

Following incidental observations in individual patients, we systematically investigated the influence of increased hyperventilation on TOR and found clear evidence of an effect of P_aCO_2 on TOR. Patients were categorized in two groups, dependingon whether they responded in the initial 24 hours after injury with a reduced TOR after increased hyperventilation or not.(chapter 4) The so-called "responders" had a statistically significant worse outcome compared to the "non-responders". An explanation for this observation could be that O_2 regulatory mechanisms are less sensitive to posttraumatic disturbances than CO_2 reactive mechanisms. The change in TOR after increased hyperventilation is not likely to be caused by a changing in metabolic rate of oxygen, but is more likely due to a change in oxygen offer. The oxygen offer to the brain is determined by the oxygen content of the arterial blood and the CBF. The oxygen content of the blood in itself is determined by the oxygen saturation of hemoglobin, which is almost always near 100%, and the free dissolved amount of oxygen in the plasma, which is represented by the arterial PO_2. The arterial PO_2 remains constant during increased hyperventilation, so no gross changes are observed in the oxygen content of the arterial blood. Rapid changes in oxygen offer are therefore due to changes in CBF caused by changes in the diameter of the regulating vessels.
Support for this hypothesis is given in chapter 4. The induced changes in $P_{br}O_2$ by changing the arterial PCO_2 are small, but similar for both outcome groups (favorable versus unfavorable), resulting in the same $CO_2/P_{br}O_2$ reactivity,(chapter 5) reflecting similar sensitivity of the regulating arteriolae to changes in arterial PCO_2 for both outcome groups. If a greater degree of dilation of the CO_2/O_2

sensitive arteriolae in the unfavorable outcome group exists after injury, decreasing arterial PCO_2 may restore arterial vascular tone to a more normal situation, and TOR tests then performed will show a more normal response. The increase of arterial PO_2 will further induce normalisation of the vascular tone (the regulating arteriolae are insensitive for changes in P_aO_2). In this situation oxygen offer is normalised by a general reduction in vessel diameter by the supplying vessels. An increase in arterial PO_2 and a decreased in arterial PCO_2 are in fact working synergetic. This situation is represented in patients with an unfavorable outcome.

To the contrary, in patients with a favorable outcome, the supplying arteriolae have a normal diameter/vascular tone, and still have an intact sensitivity for changing arterial PO_2 and PCO_2 levels. Reduction in arterial PCO_2 will therefore result in a reduction of arteriolar diameter below the normal diameter, and thus in a reduction in ICP and $P_{br}O_2$. If in this situation arterial PO_2 is increased this will not lead towards a further reduction in arteriolar diameter/oxygen supply, otherwise a critical diameter of the supplying vessel will be reached and $P_{br}O_2$ levels may reduce to subnormal values. Intact O_2 reactive mechanisms will keep the $P_{br}O_2$ levels within certain values and therefore arteriolar constriction as reaction on an increasing arterial PO_2 is less extensive, finally resulting in minimal changes in TOR.

This leads to an only minimally reduced TOR under increased hyperventilatory conditions, in patients with a favorable outcome. Alternatively it may hypothosized that the reduced TOR observed following increased hyperventilation in patients with poorer outcome may indicate a decrease of oxygen offer to more critical levels, thus indicating an increased risk of ischemia. Further research will be necessary to clarify the pathophysiologic mechanisms underlying these observations and their clinical implications.

If O_2 regulating mechanisms are less sensitive to posttraumatic changes than CO_2 reactive mechanisms during the initial period after trauma the difference in relationship between TOR and outcome and CO_2 reactivity and outcome in the same group of patients is explained. In case differences between the investigated groups are considerable, as in TOR, the number of studied patients can be small and still significancy can be reached. In case CO_2 reactivity is more or less equally disturbed in both outcome groups no significant difference will be found in the same number of studied patients.

The different relation between TOR and outcome and CO_2 reactivity and outcome may be explained if oxygen regulatory mechanisms are less sensitive to posttraumatic changes than CO_2 reactive mechanisms during the initial period after trauma. The differences in TOR observed between investigated groups were much more pronounced than those observed in CO_2 reactivity and statistical significancy was found despite a relatively small number of patients studied. Disturbances in CO_2 reactivity (absent or very low response) were probably more frequent and equally disturbed in both outcome groups with no significant differences found in the same number of patients studied.

8.4 Epilogue

In conclusion locally measured $P_{br}O_2$ reflects the global oxygenation after TBI, if measured in a relatively healthy part of the brain.
Initial low $P_{br}O_2$ values after TBI are a real phenomenon, reflecting a reduced CBF, possibly due to an increased vascular resistance in the microvascular or venous vascular bed and are not a result of an artifact. Low values up to 2 hours after insertion of the catheter can be artificial, due to minimal local brain trauma caused by the insertion itself.
Duration and depth of the $P_{br}O_2$ reduction during the first 24 hours after TBI are an independent prognostic factor for outcome 6 months after injury.
During the first 24 hours after TBI CO_2 as well as O_2 regulating mechanisms are disturbed. O_2 regulating mechanisms are less sensitive to posttraumatic changes than CO_2 regulating mechanisms. Disturbances of O_2 regulating mechanisms have an independent predictive value for outcome.
Though almost all observations can be explained by the above mentioned hypothesis, the role of a disturbed oxygen metabolism and its exact mechanism remains unclear. Further research, to my opinion, should be directed, towards the metabolic side. Combination of local $P_{br}O_2$ measurements and microdialysis, PET or functional MRI, preferably performed in the very early phase after TBI, may help to elucidate the role of oxygen metabolism and regulation during this initial period after injury. Results from such studies would hopefully provide opportunities for more targeted approaches in individual patients.

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Summary

The **first Chapter** is an introduction to neurotraumatology. The incidence of severe head injury, and its financial burden to society is described. General information is provided on the currently used monitoring modalities in patients with severe head injury. Finally a description is given of the polarographic monitoring method for measuring oxygen tension in brain tissue (PbrO2) used in our studies. The study questions are specified focussing on clinical applicability of PbrO2 measurements in TBI and interpretation of findings.

In **Chapter 2** preliminary experience with brain tissue PO_2 ($P_{br}O_2$) monitoring in a group of 22 patients with a severe head injury is described. $P_{br}O_2$ was measured with a polarographic microcatheter. For introduction of the catheter a specially devised intracranial bolt was used. Measurements started as soon as possible after the injury and the study protocol specified an observation period of a maximum of 120 hours post trauma. The rationale for this time period was that during the initial period after trauma low Cerebral Blood Flow (CBF) values have been reported with Xe CT studies, and that vasospasm mostly occurs before day 5 after injury. Both potential ischemic phenomena are covered by the observation period chosen. During the observation period two provocation tests were included in the study protocol performed on a dayly basis. Firstly, an O_2 provocation test, by increasing the fraction of inspired oxygen stepwise to 1.0, and secondly a carbon dioxide reactivity test performed by increasing the respiratory minute volume of the patient by 20%. The observation period was preliminary terminated by early death or if clinical improvement of the patient occurred to an extent that ICP monitoring was no longer considered necessary. $P_{br}O_2$ monitoring was started on average 7.0 hours after trauma with a mean duration of 74.3 hours. The chapter provides an extensive description of all phenomena observed. No complications were seen related to the $P_{br}O_2$ catheter. The catheters showed a zero display error of 1.2 ± 0.8 mmHg and a sensitivity drift of 9.7 ± 5.3% after the measurement period.

The first approach to analyse the $P_{br}O_2$ value was to average all PO_2 values according to the time after injury. Using this method of analysis we observed low average values during the initial 24 hours after injury, increasing toward a peak value during the second 24 hours reaching a plateau value after 36-48 hours after injury. Beyond this time period mean $P_{br}O_2$ showed no further changes. This

observation was in concordance with the observations on CBF made with the Xe CT technique.

Patients were categorised into two groups, according to the GOS at 6 months after injury; dichotomized into favorable outcome (MD/GR) and unfavorable outcome (D/VS/SD). Initially low values ($P_{br}O_2$ < 5 mmHg) occurred more frequently in the group of patients with an unfavorable outcome (P=0,04, Fischer exact test). $P_{br}O_2$ values < 5mmHg beyond this initial period often preceded brain death.

In analysing the oxygen provocation tests, O_2 reactivity was defined as:

$$\frac{\Delta P_{br}O_2}{\Delta P_aO_2} \times \frac{1}{P_{br}O_2(\text{baseline})} \times 100\%.$$

Results showed a linear association between arterial and cerebral PO_2 (mean R=0.93 ± 0.13), but the slope of the regression line changed within patients dependent to the time after injury and was different between individual patients. Association was observed between outcome and initial O_2 reactivity. Patients with an unfavorable outcome showed a statistically significant higher O_2 reactivity compared to patients with a favorable outcome (P=0.0003), particularly during the initial 24 hours after injury.

Analysis of the CO_2 reaction tests showed a dependency of $P_{br}O_2$ to arterial CO_2. Decreasing P_aCO_2 induced a decrease in $P_{br}O_2$. A time related tendency in mean CO_2 reactivity values was observed, with initial low values increasing the observation period. No association between CO_2 reactivity and outcome was observed.

Furthermore the chapter describes the occurence of spontaneous fluctuations in $P_{br}O_2$ for which no clear explanation could be given and describes the relationship between $P_{br}O_2$ and SjO_2 in more detail. Mean correlation between $P_{br}O_2$ and SjO_2 was 0.35 ± 0.25, but varied substantially within and between patients.

It is concluded that direct $P_{br}O_2$ measurement constitute a promising new monitoring method. The technique is considered save and free of technical artefacts. Initial $P_{br}O_2$ values are frequently low, and initially low values are related to outcome 6 months after injury. O_2 regulation appears to be disturbed, during the first 24 hours after trauma, prompting further studies on this topic.

Chapter 3 describes the full results of $P_{br}O_2$ monitoring in 101 patients with a severe head injury studied prospectively. The study focuses on the occurrence, depth, and duration of initial low values and their relation to clinical and CT characteristics as well as to outcome. The larger number of patients included in this study permitted a more detailed statistical analysis, compared to chapter 2.

$P_{br}O_2$ monitoring was started with a mean interval of 7.0 ± 3.5 hours after trauma and continued for a mean duration of 86 hours. In this larger series also no catheter related problems were observed. Post measurement calibration of the catheter showed a negligible zero display error and sensitivity drift. Time course of the averaged $P_{br}O_2$ values confirmed the frequent occurrence of initially low values, with 42% of the patients showing values < 10 mmHg during the initial 24 hours after trauma, unrelated to documented hypoxia on admission. Because the question rose whether the initial low values were possibly related to insertion trauma of the catheter, the run-in time was analysed by insertion of a second $P_{br}O_2$ catheter. The run-in time showed to be less than 2 hours in all cases studied.

Low values (< 10 mmHg) for a cumulative period of more than 30 minutes during the first 24 hours after injury had an independent predictive value for unfavorable outcome and death with respective odds ratio's of 2.8 (P=0.015) and 3.8 (P=0.002). These initial low $P_{br}O_2$ values were not related to any clinical parameter, and on analysis of the relation to CT characteristics only a relatively weak but significant association was observed to compression of the basal cisterns. We concluded that $P_{br}O_2$ can be monitored reliably with a polarographic microcatheter in the clinical setting and that, if the catheter is placed in an undamaged region of the brain and local complicating factors are absent, the recorded values may be considered representative of global oxygenation. Depth and duration of low values within 24 hours after injury were independently related to unfavorable outcome and death. We further concluded that $P_{br}O_2$ measurements can provide useful information in support of more targeted therapy in patients with a severe head injury suffering ischemic periods.

Chapter 4 describes further results on O_2 reactivity in a group of 41 patients with severe head injury. We chose to rename O_2 reactivity into brain Tissue Oxygen Response (TOR). During the initial period of the study TOR was studied with "multi step" procedures, in which the inspired fraction of O_2 was increased stepwise by fractions of 20% up to 1.0. In this first cohort of 22 patients a linear association between P_aO_2 and $P_{br}O_2$ was found (chapter 2). These findings prompted us to change our policy in TOR procedures and to adopt a "one step" procedure, in which the inspired fraction of oxygen was immediately increased from the baseline values to 1.0. The influence of increased hyperventilation of TOR was further investigated. A linear logistic regression model showed that there was little dependency of TOR to other measured parameters. Only a weak association between TOR and age and TOR and ICP/CPP was observed, with respective Pearson correlation coefficients of 0.20 and 0.18/-0.24.

Three distinct patterns of response of $P_{br}O_2$ on increasing P_aO_2 were observed, pattern A was characterised by $P_{br}O_2$ reaching a plateau, pattern B by absence of a plateau, and pattern C by a "break through phenomenon". A statistically significant time related dependency was observed. Patterns B and C were more frequently seen during the first two days after trauma and pattern A beyond the first 48 hours. A tendency towards more favorable outcome was observed if pattern A was present within the first 24 hours after injury.

For analysis of the relation between TOR and outcome patients were dichotomized into two groups according to the GOS 6 months after injury. Patients with an unfavorable outcome had a statistically significant higher TOR during the first 24 hours after injury than patients with a favorable outcome (P=0.02). The odds ratio for unfavorable outcome was 4.8 and for mortality 2.8. Logistic regression analysis supported the independent prognostic value of the TOR during the first 24 hours after injury.

During this period the P_aCO_2 level was of influence on the TOR value in patients with an unfavorable outcome. We observed a reduction of TOR following increased hyperventilation. In patients with a favorable outcome TOR was not changed or only to a much lesser extent following increased hyperventilation.

In the discussion we review existing knowledge of O_2 regulatory mechanisms in healthy volunteers and the disturbance of CO_2 reactivity after severe head injury and its relation to outcome. It is concluded that O_2 regulatory mechanisms are disturbed in the initial phase after injury, most pronounced in patients with an unfavorable outcome, also being reflected in the patterns of response observed. Mitochondrial dysfunction or vasoparalysis or possibly a combination of these factors may explain the higher TOR in patients with an unfavorable outcome. The influence of decreasing P_aCO_2 on TOR as observed in patients with an unfavorable outcome may be explained by a reduction of arteriolar diameter of the regulatory vessels to critical levels. Further studies were advised to confirm the observed results.

In **Chapter 5** the effect of hyperventilation on $P_{br}O_2$ is investigated in greater detail. Ninety patients with a severe head injury were studied prospectively. The respiratory minute volume was increased by 20% above baseline during a 15-minute period in daily interventions. CO_2 reactivity was defined as:

$$\frac{\Delta P_{br}O_2}{\Delta P_aCO_2} \times \frac{1}{P_{br}O_2 \text{ (baseline)}} \times 100\%.$$

On average hyperventilation induced a decrease in $P_{br}O_2$ of ± 1 mmHg per torr change in P_aCO_2, but varied substantially between patients. Even small reductions in P_aCO_2 could induce pronounced reductions in $P_{br}O_2$ in some patients. As such, these results provide further evidence for the potential risk of hyperventilation in causing ischemic damage. CO_2 reactivity was strongly dependent on the time period at which the studies were performed, being low on day 1 and increasing significantly over time till day 5 after trauma. The increasing CO_2 reactivity was explained by a changing sensitivity of regulating vessels to arterial CO_2. The influence of baseline P_aCO_2 on CO_2 reactivity was investigated, but no significant influence was observed, which was reflected in a linear association between absolute and relative CO_2 reactivity. The relative CO_2 reactivity was preferred above the absolute reactivity, because it theoretically corrects for initial low $P_{br}O_2$ values, and permits better comparison to CO_2 reactivity measured with TCD and CBF studies. The relation between outcome and CO_2 reactivity was studied, but contrary to our expectations no significant relation could be observed. The small changes of P_aCO_2, the great number of already mildly hyperventilated patients under baseline conditions and the relatively small number of patients may have contributed to our failure to find a clear relation.

In **Chapter 6** we tried to validate the $P_{br}O_2$ measurements with Single Photon Emission Computed Tomography (SPECT) using HMPAO. In a cohort of 17 patients with a severe head injury, serial SPECT studies were performed on day 1, day 6 and day 14 after injury in addition to $P_{br}O_2$ monitoring for the duration of the study protocol. CT scans were made on admission, 24 hours and 14 days after trauma and on clinical indication. In accordance with our intent to measure local $P_{br}O_2$ in a relatively undamaged area of the brain, supposing that this local area would be representative of global oxygenation, we determined the relative CBF (rCBF) in a Region of Interest (ROI) around the $P_{br}O_2$ catheter tip and the rCBF in the global supratentorial region. rCBF was calculated relating supratentorial HMPAO uptake (global or in the defined ROI) to the total infratentorial HMPAO

uptake. A time related tendency was observed for both the rCBF in the frontal ROI ipsilateral to the catheter and the global supratentorial rCBF, with lower initial values during the first SPECT study compared to the second and third SPECT studies. Comparing the rCBF in the region of the catheter tip and the global supratentorial rCBF no statistically significant differences could be observed, at any time after injury. This supported our hypothesis that local measurements could be considered representative of the global situation. Equally important was the question whether the $P_{br}O_2$ catheter tip was really positioned in the part of the brain without structural pathology or CBF disturbances. For this reason we compared the number and location of lesions either visible on CT or SPECT. It turned out that in this study, CT scanning demonstrated more lesions in the acute phase after injury in the frontal region than SPECT scanning. It was concluded that structural/anatomical lesions, which were adquately detected by CT, were the main causes of regional disturbances in CBF in the acute phase after trauma. In absence of such lesions near the $P_{br}O_2$ catheter measurements were indeed performed in relatively undamaged areas without focal CBF disturbances. In later phases after injury however some lesions were detected on SPECT, which were not visible on CT scanning.
In 23 SPECT studies simultaneous $P_{br}O_2$ measurements were available. In 15 patients during the first SPECT study and in 8 patients during the second SPECT study. The relation between rCBF ipsilateral to the $P_{br}O_2$ catheter and $P_{br}O_2$ was weak but statistically significant during the first SPECT study.($R=0.51$; $P=0.05$). No relation could be observed between the global rCBF and the $P_{br}O_2$, although a weak tendency was observed between low $P_{br}O_2$ values and low rCBF values.
The limitations of this study are discussed in the last paragraph of this chapter. Inadequate determination of the frontal ROI, lack of spatial resolution of the SPECT studies, supposed arterio-venous shunting, and the difference in time window for determination of the $P_{br}O_2$ and rCBF were mentioned. Moreover, $P_{br}O_2$ provides absolute and SPECT studies relative values with HMPAO reflecting CBF (oxygen offer) and $P_{br}O_2$ reflecting the balance between oxygen offer and demand. All these reasons could be responsible for the weak correlation between rCBF and $P_{br}O_2$.
Chapter 7 describes a prospective study of 57 severe head injured patients, which were studied with repeated TransCranial Doppler (TCD) studies until 10 days after trauma. In 24 patients three TCD studies were performed during the first 24 hours and two TCD studies during the second 24 hours after trauma. Mean flow velocity in the middle cerebral artery (mVmca) and internal carotid artery (mVica) were measured, and the Pulsatilty Index and the ratio between the two mean velocities were calculated. A Low Flow Velocity State (LFVS) was defined as a mVmca $\leq$ 35 cm/s in one or both MCA's within 72 hours after injury. A High Flow Velocity State (HFVS) was defined as a mVmca > 100 cm/s in one or both MCA's during at least two subsequent measurements. Patients were classified into two groups according to the admission CT scan: Patients with primarily unilateral pathology and patients with primarily diffuse or bilateral pathology. In the group of patients with unilateral pathology a lesion (L) and a Non-Lesion (NL) side could be distinguished. In 33 patients simultaneous $P_{br}O_2$ recordings until 5 days after trauma were available.

Time course of the average mVmca values showed initial low values, especially at the lesion side, increasing towards normal values on day 3 after trauma. This increase was statistically significant. Initial low mVmca values were accompanied by high PImca values. During the first 8 hours after injury the average mVmca values at the lesion side were significantly lower compared to the average mVmca values at the Non Lesion side and the average mVmca values for the diffuse group. A LFVS was frequently observed (63%) in the whole group, significantly more frequently in patients with unilateral pathology than in patients with diffuse or bilateral pathology. Significant relations were found between the occurrence of a LFVS and the initial GCS, age, occurrence of traumatic subarachnoid hemorrhage on the initial CT-scan, the degree of midline shift, CT classification and outcome. In 18% of the patients a HFVS was observed, no significant correlation was observed between a HFVS and clinical or CT parameters. The occurrence of an increased Lindegaard index was strongly related to a HFVS. During the first 8 hours after injury a very strong association was found between $P_{br}O_2$ values and the mVmca at the non lesion side, the mVmca in patients with diffuse or bilateral pathology. Beyond this time period no association was observed between mVmca and $P_{br}O_2$.
Initial low mVmca values were interpreted as low CBF, which is in concordance with the results obtained with more formal CBF studies. The lower the mVmca value the lower the CBF and oxygen offer to the brain, as reflected by the linear association between mVmca and ipsilatral $P_{br}O_2$. The associated of low mVmca values with high PI indexes suggest a high peripheral resistance. Clinical implications of this study are that early TCD measurements following TBI may detect patients with increased risk for ischemia, consequently opening opportunities for more targeted therapeutic approaches.
In **Chapter 8** a general pathofysiological concept is given in which all the results are combined. It is hypothesized that the low initial CBF values are due to a high peripheral vascular resistance, mainly caused by collapse of the venous system. Due to impending ischemia the regulating arteries are maximally dilated. In patients with an unfavorable outcome the regulating vascular mechanisms are more disturbed, such as CO_2 and O_2 reactive mechanisms. The role of these disturbances in regulating mechanisms in combination with a reduced Oxygen metabolism due to mitochondrial dysfunction remains unclear. Further research of $P_{br}O_2$ measurements in combination with microdialysis, PET and/or funtional MRI may answer these remaining questions.

Samenvatting

Het **eerste Hoofdstuk** bevat een introductie in de neurotraumatologie. Het beschrijft de incidentie van het ernstig schedelhersenletsel en de financieel economische last die de zorg voor deze patiënten met zich meebrengt. Tevens worden de thans gebruikelijke bewakingsmethodieken voor patiënten met een ernstig schedelhersenletsel beschreven. Tot slot wordt de nieuwe bewakingsmethode met een polarografische microkatheter die in dit onderzoek wordt gebruikt beschreven, en de onderzoeksvragen die ten grondslag liggen aan de beschreven studies.

In **Hoofdstuk 2** worden de eerste klinische resultaten beschreven van hersenweefsel PO_2 ($P_{br}O_2$) bewaking bij een groep van 22 patiënten met een ernstig schedelhersenletsel. $P_{br}O_2$ werd met behulp van een polarografische mikrokatheter gemeten. De katheter werd via een speciaal hiervoor ontworpen intracraniële schroef in het hersenparenchym ingebracht. De metingen startten zo snel als mogelijk na het ongeval en het studieprotocol voorzag in een maximale meetduur van 120 uur na het ongeval. De reden om voor dit tijdsinterval te kiezen was dat gedurende de eerste periode na een ongeval lage Cerebral Blood Flow (CBF) waarden werden gemeten met Xe CT technieken, en dat vasospasme meestal optreedt binnen 5 dagen na het ongeval. Beide potentieel ischaemische gebeurtenissen worden gedekt door deze meetduur. Gedurende de meetperiode werden elke dag, volgens protocol, twee provocatie testen uitgevoerd. Als eerste een O_2 provocatie test, door stapsgewijs verhogen van de FiO_2, als tweede een CO_2 reactie test, door verhoging van het adem-minuut-volume van de patiënt met 20%. De metingen werden voortijdig beëindigd indien de patiënt kwam te overlijden binnen de gestelde periode of ten gevolge van klinische verbetering, waardoor ICP bewaking overbodig werd. De $P_{br}O_2$ metingen startten gemiddeld 7.0 uur na het ongeval, de gemiddelde meetduur was 74,3 uur. Het hoofdstuk biedt een uitgebreide beschrijving van al de geobserveerde fenomenen. Er werden geen katheter gerelateerde complicaties waargenomen. De katheters werden na beëindigen van de meting geijkt en hadden een gemiddelde nulpunt afwijking van 1,2 ± 0,8 mmHg en een gemiddelde gevoeligheidsverschuiving van 9,7 ± 5,3%.

De eerste manier waarop de resultaten werden geanalyseerd was door alle $P_{br}O_2$ waarden te middelen in relatie tot het ongevalstijdstip, waarbij het ongevalstijdstip

als nulpunt werd gekozen. Door gebruik te maken van deze analysemethode werden gedurende de eerste 24 uur na het trauma gemiddeld lage $P_{br}O_2$ waarden gevonden, welke gedurende de tweede 24 uur na het trauma toenamen totdat een plateau werd bereikt gemiddeld 36-48 uur na het ongeval. Na deze periode veranderde de gemiddelde $P_{br}O_2$ niet meer. Deze bevindingen zijn in overeenstemming met de resultaten gevonden met Xe CT technieken.
Aansluitende werden de patiënten, afhankelijk van de GOS 6 maanden na het ongeval, verdeeld in twee groepen: Patiënten met een gunstige en met een ongunstige uitkomst. Lage waarden gedurende de eerste 24 uur na het trauma ($P_{br}O_2$ < 5mmHg) werd statistisch significant vaker waargenomen bij patiënten met een ongunstige uitkomst (P=0,04, Fischer exact test). Na de eerste 24 uur na het ongeval waren $P_{br}O_2$ waarden < 5 mmHg meestal een voorbode van hersendood.
De O_2 provocatie testen werden geanalyseerd middels een als volgt gedefinieerde O_2 reactiviteit:

$$\frac{\Delta P_{br}O_2}{\Delta P_aO_2} \times \frac{1}{P_{br}O_2(\text{baseline})} \times 100\%.$$

Er werd gedurende de O_2 provocatie testen een lineaire relatie waargenomen tussen de arteriële en de cerebrale PO_2 (gemiddelde R = 0,93 ± 0,13), echter de hoek van de regressielijn veranderde met de tijd zowel binnen één patiënt als tussen de patiënten onderling. Er werd een relatie gevonden tussen de initiële O_2 reactiviteit en de uitkomst. Patiënten met een ongunstige uitkomst hadden gemiddeld een statistisch significant hogere O_2 reactiviteit dan patiënten met een gunstige uitkomst (P=0,0003). Vooral gedurende de eerste 24 uur na het ongeval waren de verschillen tussen de twee uitkomstgroepen opmerkelijk.
Bij de analyse van de CO_2 reactiviteits testen werd een relatie gevonden tussen de arteriële PO_2 en de $P_{br}O_2$. Een verlaging in de arteriële PO_2 had een verlaging van de $P_{br}O_2$ tot gevolg. Gedurende de observatie periode veranderde de gemiddelde CO_2 reactiviteit, met lage waarden in het begin opklimmend tot aan het eind van de observatie periode. Er werd geen relatie gevonden tussen de CO_2 reactiviteit en de uitkomst.
Voorts beschrijft het hoofdstuk de relatie tussen de $P_{br}O_2$ en de SjO_2 en spontane fluctuaties in de $P_{br}O_2$, zonder dat hier een verklaring voor kon worden gevonden. De gemiddelde relatie tussen $P_{br}O_2$ en SjO_2 was 0,35 ± 0,25, en varieerde aanzienlijk tussen de patiënten.
Geconcludeerd werd dat de directe meting van $P_{br}O_2$ een veelbelovende nieuwe bewakingsmethodiek is. De techniek is veilig en betrouwbaar en zonder technische artefacten. $P_{br}O_2$ waarden direct na het trauma gemeten zijn meestal laag, en zeer lage waarden in de beginperiode na het trauma correleren met de uitkomst 6 maanden na het trauma. Bovendien werd vastgesteld dat het O_2 regulerend vermogen in de beginperiode na het ongeval is verstoord. Om de beschreven resultaten te bevestigen werd verder onderzoek geadviseerd.
Hoofdstuk 3 beschrijft de resultaten van 101 prospectief onderzochte patiënten met een ernstig schedelhersenletsel, waarbij $P_{br}O_2$ metingen werden verricht. De studie beschrijft met name de relatie tussen optreden, ernst en duur van de initieel lage waarden en de CT parameters, klinische karakteristieken en de uitkomst. In

vergelijking met hoofdstuk 2 is een uitgebreidere statische analyse mogelijk, i.v.m. de grotere studiepopulatie.
De bewaking van $P_{br}O_2$ startte met een gemiddeld interval van 7,0 ± 3,5 uur van trauma tot start van de meting, en de gemiddelde meetduur was 86 uur. Ook nu werden geen katheter gerelateerde complicaties waargenomen. Calibratie van de katheters na de meting toonde een verwaarloosbare nulpunt en gevoeligheidsverschuiving. Het beloop in de tijd van de gemiddelde $P_{br}O_2$ waarden werd gekarakteriseerd door lage beginwaarden. 42% van de patiënten had een $P_{br}O_2$ < 10 mmHg gedurende de eerste 24 uur na het trauma, deze waarde had geen relatie met gedocumenteerde hypoxie bij opname. Door een tweede katheter te plaatsen enkele uren na plaatsing van de eerste $P_{br}O_2$ katheter werd de inlooptijd van de katheter geanalyseerd, dit omdat er enige discussie bestond of de lage beginwaarden te wijten zouden kunnen zijn aan lokale schade na inbrengen van de katheter. De inlooptijd bleek in alle gevallen minder dan 2 uur te zijn.
Lage waarden (< 10 mmHg) over een cumulatieve periode van meer dan 30 minuten gedurende de eerste 24 uur na het trauma hadden een onafhankelijk voorspellende waarde ten aanzien van een ongunstige uitkomst en overlijden. De odds ratio's waren respectievelijk 2,8 (P=0,015) en 3,8 (P=0,002). De lage beginwaarden hadden geen relatie met klinische parameters, de enig significante relatie die werd gezien was een relatie met de toestand van de basale cisternen op de opname CT.
We kwamen tot de conclusie dat bij patiënten $P_{br}O_2$ veilig kan worden gemeten met een microkatheter. Als de katheter wordt gepositioneerd in een relatief onbeschadigd gebied van de hersenen en er geen lokaal complicerende factoren aanwezig zijn, dan kunnen de gemeten waarden representatief worden geacht voor de meer globale cerebrale oxygenatie. Ernst en duur van lage waarden binnen 24 uur na het trauma gemeten vormen een onafhankelijk voorspellende parameter voor een ongunstige uitkomst en overlijden. Dientengevolge kan de bewaking van $P_{br}O_2$ nuttige aanvullende informatie leveren voor een meer doelgerichte therapie van patiënten met een ernstig schedelhersenletsel, die "at-risk" zijn voor cerebrale ischaemie.
Als aanvulling op de geleverde informatie in hoofdstuk 2, wordt in **Hoofdstuk 4** een groep van 41 patiënten beschreven met een ernstig schedelhersenletsel, waarbij de O_2 reactiviteit wordt onderzocht. De O_2 reactiviteit wordt een nieuwe term gegeven nl: Brain Tissue Oxygen Response (TOR). De TOR werd in de eerste fase van de studie (hoofdstuk 2) onderzocht met een zogenaamde "multi-step" test, waarbij de FiO_2 stapsgewijs werd verhoogd met 20%, tot 1,0. In de eerste groep van 22 patiënten werd een lineaire relatie gevonden tussen de PaO_2 en de $P_{br}O_2$. Dit gegeven veranderde ons beleid t.a.v. de TOR test, er werd overgegaan op de zogenaamde "one-step" test, waarbij de FiO_2 van de uitgangswaarde in één keer werd verhoogd tot 1,0. Tevens wordt de invloed van een veranderende $PaCO_2$ op de TOR in dit hoofdstuk beschreven. Vanwege de toegenomen omvang van de studiepopulatie kon ook nu weer een meer uitvoerige statische analyse plaatsvinden in vergelijking met hoofdstuk 2.
Met behulp van een lineaire regressie analyse kon worden aangetoond dat TOR nagenoeg onafhankelijk is van andere gemeten parameters. Slechts een zeer geringe

relatie tussen TOR en ICP/CPP en leeftijd werd gevonden, met respectievelijke Pearson correlatie coëfficiënten van 0,18/-0,24 en 0,20.
Bij de TOR procedure werden drie verschillende $P_{br}O_2$ reactie patronen herkend. In patroon A bereikt de $P_{br}O_2$ een plateau, patroon B zonder een plateau waarde voor de $P_{br}O_2$, en patroon C met een soort 'break through" fenomeen. De reactie patronen hadden een statistisch significante relatie met de tijd, waarbij patroon B en C meer frequent werden waargenomen gedurende de eerste 2 dagen na het trauma en patroon A juist meer in de periode hierna. Wanneer alleen werd gekeken naar de eerste 24 uur na het trauma kon een trend worden waargenomen waarbij een relatie bestaat tussen patroon A en een gunstige uitkomst.
Ook werd de relatie tussen TOR en uitkomst bestudeerd. De groep patiënten werd onderverdeeld in twee groepen afhankelijk van de GOS 6 maanden na het trauma gemeten. Patiënten met een ongunstige uitkomst hadden een statistisch significant hogere TOR gedurende de eerste 24 uur na het trauma dan patiënten met een gunstige uitkomst (P=0,02). De odds ratio voor een ongunstige uitkomst was 4,8 en 2,8 voor overlijden. Logistische regressie analyse ondersteunde de onafhankelijk voorspellende waarde van de TOR gedurende de eerste 24 uur na het trauma.
Gedurende de eerste 24 uur na het trauma was de P_aCO_2 van invloed op de TOR in de groep patiënten met een ongunstige uitkomst. Bij deze patiënten groep induceerde een verlaging van de P_aCO_2 een statistisch significante verlaging in TOR. Bij patiënten met een gunstige uitkomst was de P_aCO_2 minder van invloed op de TOR waarde.
In de discussie wordt aandacht besteed aan de beschikbare kennis over O_2 regulerende mechanismen van de hersenen bij gezonde vrijwilligers en aan de verstoring van de CO_2 reactiviteit na een ernstig schedelhersenletsel en de relatie tot de uitkomst. Er wordt geconcludeerd dat de O_2 regulerende mechanismen verstoord zijn in de initiële fase na het trauma, vooral bij patiënten met een ongunstige uitkomst. Mogelijk dat de waargenomen reactie patronen hiervan een afspiegeling vormen. Vasoparalyse of mitochondriale dysfunctie of een combinatie van deze twee factoren kunnen een verklaring zijn voor de hogere TOR bij patiënten met een ongunstige uitkomst. De invloed van een dalende P_aCO_2 op de TOR bij patiënten met een ongunstige uitkomst wordt verklaard op grond van een reductie in diameter van de regulerende arteriolen tot mogelijk een kritisch nivo. Er wordt geadviseerd om dit in aanvullende studies te bevestigen.
In **Hoofdstuk 5** wordt op uitgebreide wijze het effect van hyperventilatie op de $P_{br}O_2$ onderzocht. Negentig patiënten met een ernstig schedelhersenletsel werden prospectieve onderzocht. De CO_2 reactiviteit werd dagelijks onderzocht door het adem-minuut-volume gedurende een periode van 15 minuten te verhogen met 20%. CO_2 reactiviteit werd als volgt gedefinieerd:

$$\frac{\Delta P_{br}O_2}{\Delta P_aCO_2} \times \frac{1}{P_{br}O_2 \text{ (baseline)}} \times 100\%.$$

In het algemeen induceerde hyperventilatie een daling van $P_{br}O_2$ van 1 mmHg per 1 mmHg P_aCO_2, maar de reactie verschilde aanmerkelijk tussen de patiënten. Een geringe vermindering in P_aCO_2 kon zelfs een grote daling in $P_{br}O_2$ tot gevolg hebben. Als zodanig geven deze gegevens additioneel bewijs voor het potentiële gevaar dat hyperventilatie ischaemie kan induceren. De CO_2 reactiviteit was sterk

afhankelijk van het tijdstip na trauma waarop de test werd afgenomen. De CO_2 reactiviteit was laag op de eerste dag na het ongeval en steeg gedurende de observatie periode statistisch significant tot dag 5 na het trauma. De toename van de CO_2 reactiviteit in de loop van de tijd werd verklaard door een toename van de gevoeligheid van de regulerende arteriolen op CO_2. De beginwaarde van de P_aCO_2 bleek niet van invloed op de CO_2 reactiviteit, hetgeen ook tot uiting komt in een lineaire relatie tussen absolute en relatieve CO_2 reactiviteits waarden. Toch wordt de voorkeur gegeven aan de relatieve CO_2 reactiviteit boven de absolute reactiviteit, omdat in theorie de relatieve CO_2 reactiviteitwaarde corrigeert voor lage $P_{br}O_2$ uitgangswaarden, bovendien wordt de vergelijking met de CO_2 reactiviteit gevonden met TCD en CBF studies mogelijk. De relatie tussen CO_2 reactiviteit en uitkomst werd onderzocht maar er werd geen significantie relatie gevonden. Mogelijk dat de kleine veranderingen in $PaCO_2$, het grote aantal patiënten dat reeds voor de start van de reactiviteits test werd gehyperventileerd of het relatief kleine aantal patiënten dat werd onderzocht hieraan ten grondslag ligt.

In **Hoofdstuk 6** wordt gepoogd de $P_{br}O_2$ waarde te valideren middels Single Photon Emission Computed Tomography (SPECT) met HMPAO. In een cohort van 17 patiënten met een ernstig schedelhersenletsel, werden SPECT studies verricht op dag 1, dag 6 en dag 14 na het ongeval, naast het feit dat er volgens protocol gedurende 5 dagen $P_{br}O_2$ werd gemeten. CT scans werden bij opname in het ziekenhuis gemaakt, 24 uur na het ongeval en 14 dagen na het ongeval, bovendien wanneer het medisch geïndiceerd was. De gedachte om $P_{br}O_2$ te meten in een relatief gezond deel van de hersenen gaat van de veronderstelling uit dat dit deel representatief is voor de rest van het niet geleadeerde deel van de hersenen. Hiervan uitgaande bepaalden we de relatieve Cerebral Blood Flow (rCBF) in een Region of Interest (ROI) rond de tip van de $P_{br}O_2$ katheter (lokale rCBF) en de rCBF in het supratentoriele gebied, de globale rCBF. De rCBF werd berekend door de opname van HMPAO in het gebied van interesse te delen door de opname van HMPAO in het infratentoriele gebied.

Een verandering over de tijd werd geobserveerd in de rCBF voor zowel de lokale rCBF als globale rCBF, met lagere waarden op dag 1 na het trauma in vergelijking met de waarden gevonden op dag 6 en 14 na het trauma. Er werden geen statistisch significante verschillen gevonden in de lokale en globale rCBF, onafhankelijk van het tijdstip na het trauma. Deze bevinding ondersteunen de hypothese dat een lokale meting kan dienen als representant van de globale situatie. Uitgaande van het bovenstaande is het belangrijk om te weten of de tip van de katheter zich werkelijk in een gebied bevindt waar geen verstoring is van de CBF. Om deze vraag te kunnen beantwoorden vergeleken we de plaats en het aantal afwijkingen die werden gezien op CT en/of SPECT onderzoek. Het bleek in deze studie dat, CT onderzoek gevoeliger is in het opsporen van afwijkingen in de acute fase na het ongeval dan SPECT onderzoek, met name in het frontale deel van de hersenen. Als conclusie wordt hieruit afgeleid dat met name structurele/anatomische afwijkingen de CBF veranderingen in de acute fase bepalen, en deze afwijkingen worden goed in beeld gebracht met CT onderzoek. Op grond van CT onderzoek kan de $P_{br}O_2$ katheter dus betrouwbaar worden gepositioneerd. Slechts in een latere fase na het ongeval

werden enkele afwijkingen met het SPECT onderzoek waargenomen, welke niet werden gezien m.b.v. CT onderzoek.
Bij 23 SPECT onderzoekingen werd tegelijkertijd de $P_{br}O_2$ gemeten. Bij 15 patiënten gedurende de het eerste SPECT onderzoek en bij 8 patiënten gedurende het tweede SPECT onderzoek. Gedurende het eerste SPECT onderzoek was relatie tussen de lokale rCBF waarde en de $P_{br}O_2$ waarden zwak maar wel statistisch significant (R=0,51; P=0,05). Er werd geen relatie gevonden tussen de globale rCBF en de $P_{br}O_2$ meting, alhoewel een zwakke trend waarneembaar was tussen lage $P_{br}O_2$ waarden en lage rCBF waarden.
De beperkingen van het onderzoek worden besproken in de laatste paragraaf van het hoofdstuk. Het niet goed bepalen van het gebied van interesse (ROI) rond de kathetertip, het gebrek aan oplossend vermogen van het SPECT onderzoek, veronderstelde arterio-veneuze shunting en verschillen in het tijdsframe waarin de verschillende gegevens worden verzameld kunnen ten grondslag liggen aan de zwakke relatie die werd gevonden tussen $P_{br}O_2$ en lokale rCBF. Bovendien meet de $P_{br}O_2$ katheter in absolute waarden en voorziet het SPECT onderzoek in relatieve waarden. Ook het feit dat de uptake van HMPAO alleen de CBF weergeeft (= zuurstofaanbod) en dat $P_{br}O_2$ waarde de balans tussen O_2 aanbod en vraag weerspiegelt kan een reden zijn voor de zwakke relatie tussen de twee parameters.
In **Hoofdstuk 7** wordt een studie beschreven van 57 patiënten met een ernstig schedelhersenletsel, die herhaaldelijk werden onderzocht met Transcraniele Doppler (TCD), tot 10 dagen na het trauma. Bij 24 patiënten werd drie keer gemeten in de eerste 24 uur na het trauma en twee keer in de volgende 24 uur na het trauma. De gemiddelde stroomsnelheid in de arteria cerebri media (mVmca) en de arteria carotis interna (mVica) werden gemeten, bovendien werd de Pulsatility Index (PI) en de verhouding tussen de mVmca en mVica berekend. Een Low Flow Velocity State (LFVS) werd gedefinieerd als een mVmca < 35 cm/s in één of beide MCA binnen 72 uur na het trauma. Een High Flow Velocity State (HFVS) werd gedefinieerd als een stroomsnelheid van > 100 cm/s in één of beide MCA's gedurende twee of meer opeenvolgende metingen, onafhankelijk van het tijdstip na het trauma. De patiënten werden onderverdeeld in twee groepen op basis van de CT gemaakt bij opname: Patiënten met voornamelijk unilaterale pathologie en patiënten met voornamelijk bilaterale of diffuse pathologie. Bij de patiënten met unilaterale pathologie kan een onderscheid worden gemaakt tussen de kant van de laesie (L) en de niet gelaedeerde (NL) kant. Bij 33 patiënten werd gedurende 5 dagen na het trauma gelijktijdig de $P_{br}O_2$ gemeten.
Het beloop in de tijd van de gemiddelde mVmca waarden toonde lage waarden in het begin na het trauma, met name aan de kant van de laesie, welke toenamen tot normale waarden drie dagen na het ongeval. De toename van de gemiddelde mVmca was statistisch significant. De lage mVmca waarden in het begin gingen gepaard met hoge PImca waarden. Gedurende de eerste 8 uur na het trauma waren de mVmca waarden aan de kant van de laesie significant lager dan de mVmca waarden aan de niet gelaedeerde kant en de gemiddelde mVmca waarden uit de diffuse groep. Bij 63% van de patiënten werd een LFVS waargenomen. Bij patiënten met unilaterale pathologie op de CT werd statistisch significant vaker een LFVS waargenomen dan bij patiënten met een meer diffuse pathologie. Er werd een

significante relatie gevonden tussen het optreden van een LFVS en GCS bij binnenkomst, leeftijd, het voorkomen van traumatisch subarachnoidaal bloed op de CT scan (tSAH), de hoeveelheid midline shift, CT classificatie en uitkomst. Bij 18% van de patiënten werd een HFVS waargenomen. Er werden geen significante relaties gevonden tussen het optreden van een HFVS en klinische of CT parameters. Wel werd een sterke relatie gevonden tussen het optreden van een HFVS en een verhoogde Lindegaard Index.
Gedurende de eerste 8 uur na het trauma werd een sterke relatie gevonden tussen de $P_{br}O_2$ waarde en de mVmca aan de niet gelaedeerde zijde en de gemiddelde mVmca uit de diffuse groep. Na dit tijdsbestek kon geen relatie tussen de genoemde waarden meer worden aangetoond.
Lage mVmca waarden direct na het trauma worden geïnterpreteerd als een lage CBF, hetgeen in overeenstemming is met gegevens uit de literatuur gevonden met Xe CT onderzoek. Omdat een lineaire relatie wordt gevonden tussen de mVmca en de $P_{br}O_2$ moet worden aangenomen dat er ook een lineaire relatie bestaat tussen de mVmca en de CBF. De lage mVmca waarden in combinatie met hoge PImca waarden doet vermoeden dat de oorzaak ligt in een hoge perifere weerstand. Patiënten met een verhoogd risico op ischaemie kunnen mogelijk worden opgespoord met TCD in een vroeg stadium na het ongeval, hetgeen misschien een meer gerichte therapie mogelijk maakt.
In **Hoofdstuk 8** wordt een hypothese geformuleerd waarin al de resultaten van het onderzoek zijn verwerkt. Er wordt verondersteld dat de lage CBF direct na het trauma het gevolg is van een hoge perifere weerstand, welke wordt veroorzaakt door het samenvallen van het veneuze systeem. Ten gevolge van dreigende ischaemie zullen de aanvoerende arteriën zich maximaal dilateren. Bij patiënten met een slechte uitkomst zijn de regulerende mechanismen verstoord, zoals het O_2 en het CO_2 reactieve systeem dit i.t.t. patiënten met een goede uitkomst. De rol van deze verstoring in combinatie met een verstoord zuurstof metabolisme door mitochondriale disfunctie is onduidelijk. Verder onderzoek m.b.v. directe zuurstof meting in combinatie met microdialyse, PET en/of functionele MRI kunnen mogelijk antwoord geven op deze vragen.

Dankwoord

Eén van de meest gelezen delen van een proefschrift, ook ik wil gebruik maken van deze unieke gelegenheid om de diverse mensen te bedanken die hebben bijgedragen aan het tot stand komen van dit proefschrift.
Beste Prof.dr. CJJ Avezaat, beste Cees, het heeft lang geduurd, maar uiteindelijk is het er dan toch van gekomen. Jij bent mijn opleider in de neurochirurgie en hebt mij de gelegenheid gegeven om dit onderzoek te starten en uiteindelijk te voltooien. In de Rotterdamse jaren heb ik dan ook ruimschoots de tijd gehad om van jou te leren, alhoewel dat vaak niet direct gerelateerd was aan operatief handelen. Veeleer heb jij mij het gebeuren om de patiënt heen, in al zijn facetten, bijgebracht. Ik heb bewondering voor jouw geduld om telkens weer een afweging te maken als ware het de eerste keer. Het wikken en wegen in de neurochirurgie zal ook voor mij altijd één van de belangrijkste aspecten blijven. Mijn dank daarvoor.
Beste Dr. AIR Maas, Beste Andrew, zonder jou was het proefschrift zoals dat er nu ligt, nooit tot stand gekomen. In de afgelopen jaren hebben we een bijzondere relatie opgebouwd. In eerste instantie hadden we, naar mijn mening, een soort haatliefde verhouding. Op bepaalde momenten heb jij mij tot het uiterste gedreven en kon de relatie wel een positieve impuls gebruiken, gelukkig kwam die impuls vroeg of laat altijd. Gelukkig is de relatie in de loop van de tijd verbeterd. Gaandeweg de lange tijd die het tot stand komen van het proefschrift in beslag heeft genomen, heb ik meer en meer waardering voor jou gekregen en naar ik hoop jij voor mij. Nadat jij mij hebt geïntroduceerd in de neurotraumatologie, ben jij, zeker gedurende de laatste jaren van mijn opleiding, ook een ware opleider voor mij geweest. We hebben aangename donderdagen in Dordrecht beleefd en jij hebt me veel vertrouwen gegeven. Dank daarvoor.
Beste Drs. W Thijsse, beste Willy. Wat hebben wij veel gepraat over van alles en nog wat. Jij weet als geen ander hoe belangrijk dat is, zeker voor een pas beginnend assistent. Waren er frustraties, onzekerheden op welk vlak dan ook, dan had jij altijd een luisterend oor. Bovendien mocht ik op jouw afdeling de metingen verrichten zonder dat mij een haarbreed in de weg werd gelegd. Dank daarvoor.
Beste Dr. WA van den Brink, beste Wimar. Helaas zijn onze wegen gescheiden. Ik denk dat we een goed team zouden zijn geweest in de neurotraumatologie. Gedurende de opleiding en ook nog daarna hebben we talloze discussies gevoerd

over hoe het nu verder moest met de metingen, en over het feit wat echte whisky is en vooral wat niet. Zeker over dat laatste waren we het snel eens. Misschien onbewust is mede daaruit het onderhavige proefschrift voortgevloeid. Voorts heb jij, als jong staflid, mij de eerste wat grotere operaties laten doen, waarvan ik veel heb geleerd. Dank daarvoor.
Beste Mw. N Elink-Schuurman, beste Nanda, ook jij bent, op vele vlakken, onmisbaar geweest in het tot stand komen van dit proefschrift. Natuurlijk zijn jouw secretariële kwaliteiten onmiskenbaar, zoals iemand zich dat zou wensen. Ik benijd diegene waarvoor je nu werkt. Maar ook jij als overbuurvrouw hebt vele verhalen van mij aan moeten horen en ook jij deed dat zonder morren. Dank daarvoor.
Voorts de mensen op de IC, met name Wilma Janssen, Chris Hoogesteegher en Joost Vermeulen, zonder de anderen tekort te doen, hebben in grote mate bijgedragen tot het vergaren van de data. Zonder hun bereidwillige hulp, en met name in het begin het bijbrengen van de meest elementaire begrippen, was het niet gelukt. Dank.
Peter Roodzand, als technicus heb jij veel voor mij geregeld. Uiteindelijk vloeiden de data zonder enig probleem de computer in. Daarvan heb ik veel profijt gehad. Dank.
Joost Schouten, als enthousiaste student moet jij vast wel eens gedacht hebben “dat moet sneller kunnen”. Ondertussen ben je zelf onderzoeker en hoop ik voor jouw dat het ook werkelijk sneller gaat. Met de Doppler en de SPECT artikelen heb jij veel hand-en-span-diensten geleverd, waarvoor mijn dank.
José Antonio Carmona, als tropische vrucht in ons koude en natte Nederland, heb jij veel leven in de brouwerij gebracht. Jouw gedachten waren voor mij niet altijd navolgbaar, maar jouw enthousiasme en niet aflatend optimisme waren een stimulans. Dank.
Medewerkers van de nucleaire geneeskunde, die ook in het weekend SPECT studies hebben verricht bij beademde patiënten. Een nieuwe ervaring waarvoor zij zich met veel enthousiasme hebben ingezet. Technici die ons hebben geholpen met de eerste opzet van de analyse en dataverwerking. Dank.
Prof.dr EAM Beuls, best Emile, jij hebt mij gedurende de laatste jaren in de gelegenheid gesteld om het manuscript af te ronden. Dank.
Ook de collega’s van de afdeling neurochirurgie in Maastricht hebben misschien zonder het te weten bijgedragen aan de tot stand komen van het proefschrift, door mij menig maal rustig te laten werken achter de computer, allen dank daarvoor.
Dr. MJ van der Mooren, Beste Jan. Hoe moet ik jou bedanken? Eigenlijk schieten woorden tekort. Gelukkig is de afstand nooit een probleem geweest. Voor jouw zijn geen bergen te hoog of zeeën te diep, ik hoop dat we nog lange tijd zo door kunnen gaan.
Mijn vader en mijn moeder. Veel gelegenheid om jullie in het openbaar te bedanken is er niet, dus wil ik van deze gelegenheid gebruik maken. Jullie hebben tenslotte de basis gelegd, jullie thuis is voor mij belangrijk geweest. Dat kwam er natuurlijk niet altijd uit, vooral niet in de moeilijke puberale jaren. Jullie hebben ondanks alles altijd vertrouwen in mij gehad en voor mij de gelegenheid geschapen om mij te ontplooien zoals ik dat wilde. Ik vind dat knap, temeer daar jullie zelf niet in de gelegenheid zijn geweest, of door omstandigheden jullie de gelegenheid is

ontnomen om jullie te ontplooien, zoals jullie dat voor ogen hadden. Grenzeloos vertrouwen gecombineerd met oosterse nuchterheid, daar staan jullie voor, daarvoor heb ik gaandeweg meer en meer respect gekregen. Dank.
Als laatste, mijn gezin, Marianne, Vera, Wouter en Esther. Voor mijn carrière hebben jullie veel moeten laten. In eerste instantie verhuizen naar het westen van het land. Niet de eerste keus. Veel van huis, lange werkweken en beperkingen in het sociale leven waren jullie deel. Daarna de opleiding, die veel van mijn aandacht eiste die ik ondertussen niet aan jullie kon geven. We zijn door diepe dalen gegaan, maar gelukkig zijn we weer op het vlakke gekomen en lijkt het diepste dal nu aan de horizon verdwenen te zijn en gloort een goede, en vooral gezonde toekomst aan de horizon. Daarna specialist, geen ‘heaven on earth’ voor jullie. Den Haag, Amsterdam, en uiteindelijk, wie had het kunnen bedenken, Maastricht. Jullie hebben jullie vertrouwde nest voor mij verlaten. Dat gaat niet altijd zonder slag of stoot. Hopelijk krijgen we nu wat vastere grond onder de voeten en kunnen we ook aan jullie toekomst gaan bouwen. Zonder een thuis zoals jullie mij dat hebben gegeven zou het mij niet gelukt zijn. De thuishaven is en blijft de belangrijkste basis. Dank, heel veel dank daarvoor.

Curriculum Vitae

Henk van Santbrink werd geboren op 2 mei 1962, te Eibergen. Na de lagere school in Eibergen volgde hij van 1974 tot en met 1981, het VWO aan de RSG Hamaland te Winterswijk. In 1981 werd aangevangen met de studie geneeskunde aan de Katholieke Universiteit Nijmegen. Gedurende de studie is hij tweemaal een periode in Afrika geweest. In eerste instantie (1986) in Ghana, voor een student-uitwisselingsprogramma. De tweede keer in Tanzania (1988-89) in het kader van het facultatieve co-schap ontwikkelingsgeneeskunde. In de wachttijd tussen doctoraalexamen en co-scappen in werkte hij als taxichauffeur in Nijmegen. De interesse voor neurowetenschappen werd gevoed gedurende het co-schap neurologie en de wetenschappelijke stage op de afdeling nucleaire geneeskunde van het ziekenhuis de Stadsmaten (thans: Medisch Spectrum Twente), begeleiders Dr. JAG Geelen en drs. FA van der Weel. In september 1989 werd het artsexamen behaald. Van december 1989 tot februari 1991 vervulde hij zijn dienstplicht, eerst de algemeen militaire opleiding in Hollandsche Rading, later als arts-assistent revalidatie geneeskunde in het militair revalidatiecentrum Aardenburg in Doorn.
In april 1991 begon hij als AGNIO op de afdeling neurochirurgie van het Dijkzigt ziekenhuis te Rotterdam (thans Erasmus MC). Hiermee werd de basis gelegd voor de opleiding tot neurochirurg. Van april 1992 tot en met april 1994, was hij fulltime wetenschappelijk medewerker aan de Erasmus Universiteit, in deze periode werden de eerste data verzameld die ten grondslag liggen aan het proefschrift.
In mei 1994 werd aangevangen met de opleiding tot neurochirurg in het Dijkzigt ziekenhuis, opleider: Prof. Dr. CJJ Avezaat. Gedurende de opleiding werd het jaar neurologie volbracht in hetzelfde ziekenhuis (opleider: Prof. Dr. FA van der Meché) en het jaar algemene heelkunde in het Ikazia ziekenhuis (opleider: Dr. HF Veen). Per 1 mei 2000 is hij geregistreerd als neurochirurg. Van mei tot en met december 2000 heeft hij parttime gewerkt als waarnemend neurochirurg in het Westeinde ziekenhuis te Den Haag en het Reinier de Graaf Ziekenhuis in Delft, en als parttime wetenschappelijk medewerker in het EMCR, om verder te werken aan het proefschrift. Per 1 januari 2001 begon hij als staflid neurochirurgie in het Academisch Medisch Centrum, te Amsterdam. Uiteindelijk is hij vanaf november 2001 als staflid verbonden aan het Academisch Ziekenhuis Maastricht, met als aandachtsgebied de wervelkolomchirurgie.
Ondertussen is hij op 5 november 1992 getrouwd met Marianne van der Sluis en hebben zij drie kinderen gekregen, Vera, Wouter en Esther.