Doctoral Thesis

The measurement of the oxygenation status of the newborn infant

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The Measurement of the Oxygenation Status of the Newborn Infant

A dissertation submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH

for the degree of
Doctor of Technical Sciences

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1996
dedicated to my beloved wife Ursula
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1.1. Abstract

Preterm infants are frequently unable to achieve sufficient oxygenation by breathing room air. Under such circumstances they receive oxygen. Too much as well as too little oxygen can be harmful, especially for the neonatal brain. Hence the oxygenation status of the brain has to be measured. The important factors to judge the oxygenation status are the 1) cerebral haemoglobin concentration (cHbc), 2) cerebral blood flow (cbf), 3) the transit time, 4) arterial and venous oxygen saturation (SaO₂ respectively SvO₂):

1) A method to measure cHbc by near infrared spectrophotometry is described. In a clinical environment the measurements are never ideal, i.e. certain fluctuations and noise, which may affect the physical assumptions of this method, are always present. To investigate how much these fluctuations affect the reliability of the method the cHbc measurements were repeated several times in clinically stable neonates and the test retest variability was calculated. The influence of fluctuations of different parameters on the test retest variability was determined. A set of quantitative criteria to judge the quality of a single measurement is provided. This study bases this method on sound physical principles and determines its reliability.

2) Two methods to assess cbf by near infrared spectrophotometry are described. The procedure and purpose of this study are in analogy with the cHbc study.

3) A mathematical one compartment model was used to determine the transit time of blood through the brain in addition to cHbc and cbf. It showed that the transit time in preterm infants decreases with gestational age.

4) To determine the cerebral arterial and venous oxygen saturation (SaO₂ respectively SvO₂), a photometer with high time resolution was developed. Both parameters can be measured continuously. For the first time a non-invasive technique provides continuous data not only on the oxygen offered but also on the oxygen extraction, which equals to the difference between SaO₂ and SvO₂.

The establishment of the above parameters allows a full description of the oxygenation status of the newborn infant: Oxygen offer and consumption can be determined using a combination of the above parameters.
The optical techniques described are non-invasive and can be performed at the bedside. They give important information to determine how much oxygen should be given to preterm infants. **Fuzzy Logic** was applied to diagnose the condition of preterm infants using the continuous data, which is routinely available in the intensive care unit. The system was able to eliminate movement artefacts and detects critical situations reliably. It was shown that Fuzzy Logic is appropriate to monitor the oxygenation status of a patient in a clinical environment.

1.2. Zusammenfassung

Frühgeborene Kinder sind oft noch nicht fähig in Raumluft ausreichend zu atmen, das heisst ihre Sauerstoffversorgung ist ungenügend. In solchen Fällen wird die Sauerstoffkonzentration in der Atemluft erhöht. Eine zu hohe wie auch eine zu niedrige Sauerstoffkonzentration kann schädlich sein vor allem für das Gehirn. Deshalb ist es wichtig den Sauerstoffstatus des Gehirnes zu messen. Die wichtigsten Faktoren um den Sauerstoffstatus zu beurteilen sind die 1) cerebrale Hämoglobinkonzentration (cHbc), 2) der cerebrale Blutfluss (cbf), 3) die Transitzeit, 4) die arterielle und venöse Sauerstoffsättigung (SaO₂ beziehungsweise SvO₂).

1) Eine Methode zur Messung der cHbc mittels Nahinfrarotspektrophotometrie wird beschrieben. Im klinischen Umfeld sind die Messungen immer durch Fluktuationen und Rauschen gestört. Dies kann dazu führen, dass die physikalischen Voraussetzungen der Methode nicht vollständig erfüllt sind. Um zu untersuchen wie sehr dadurch die Zuverlässigkeit der Messungen beeinträchtigt wird, wurden die cHbc Messungen bei klinisch stabilen Kindern mehrmals hintereinander wiederholt und die Reproduzierbarkeit berechnet. Der Einfluss von Fluktuationen verschiedener Parameter auf die Reproduzierbarkeit wurde bestimmt. Es wurden quantitative Kriterien festgelegt, anhand derer die Qualität der einzelnen Messung beurteilt werden kann. Die hier vorliegende Studie untersucht die Zuverlässigkeit dieser Messmethode und stellt sie auf eine physikalische Grundlage.
2) Zwei Methoden um cbf mittels Nahinfrarotspektrophotometrie zu bestimmen werden beschrieben. Der Zweck und das Vorgehen bei dieser Studie sind analog zur cHbc Studie.

3) Ein mathematisches Einkompartimentmodell wurde angewendet um die Transitzeit des Blutes durch das Gehirn, zusätzlich zur cHbc und zum cbf zu bestimmen. Es zeigte sich, dass die Transitzeit mit zunehmendem Gestationsalter abnimmt.

4) Um die cerebrale arterielle und venöse Sauerstoffsättigung (SaO₂ bzw. SvO₂) zu bestimmen, wurde ein Photometer mit hoher Zeitauflosung entwickelt. Beide Parameter können kontinuierlich bestimmt werden. Zum ersten Mal ermöglicht eine nichtinvasive Methode die Ermittlung kontinuierlicher Daten nicht nur über das Sauerstoffangebot (cHbc, cbf, SaO₂), sondern auch über die Sauerstoffextraktion (SaO₂-SvO₂). Das Sauerstoffangebot und der Sauerstoffverbrauch können aus den obigen Parameter berechnet werden. Somit ist der Sauerstoffstatus vollständig bestimmt.

# 2. Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>bw</strong></td>
<td>birthweight [g]</td>
</tr>
<tr>
<td><strong>cbf</strong></td>
<td>cerebral blood flow ([\text{ml/(100g*min)}]), in ml of blood per 100g of brain per min.</td>
</tr>
<tr>
<td><strong>cbv</strong></td>
<td>cerebral blood volume ([\text{ml/100g}]) in ml of blood per 100g of brain.</td>
</tr>
<tr>
<td><strong>cHb</strong></td>
<td>haemoglobin concentration in the blood ([\text{mmol/l or g/100ml}])</td>
</tr>
<tr>
<td><strong>cHbc</strong></td>
<td>cerebral haemoglobin concentration ([\text{μmol/l}]), in μmol of haemoglobin per l of brain</td>
</tr>
<tr>
<td><strong>cHbf</strong></td>
<td>cerebral haemoglobin flow ([\text{g/(100g*min)}]), in g of haemoglobin per 100g of brain per min.</td>
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<tr>
<td><strong>cHbw</strong></td>
<td>cerebral haemoglobin weight ([\text{g/100g}]), in g of haemoglobin per 100g of brain.</td>
</tr>
<tr>
<td><strong>COP</strong></td>
<td>one particular method to calculate cerebral blood flow (see chapter 5.3.2.)</td>
</tr>
<tr>
<td><strong>CPAP</strong></td>
<td>continuous positive airway pressure, prevents the lungs from collapsing.</td>
</tr>
<tr>
<td><strong>DEL</strong></td>
<td>delay between the arterial oxygen saturation ((\text{SaO}_2)) and the oxygen index ((\text{O}_1)) curves, evolves from different sites of the sensors.</td>
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<tr>
<td><strong>DF</strong></td>
<td>degrees of freedom of a statistical model.</td>
</tr>
<tr>
<td><strong>DPF</strong></td>
<td>differential pathlength factor determines, how many times the optical pathlength, i.e. the distance the light travels through a scattering medium, is longer than the direct emitter-detector spacing.</td>
</tr>
<tr>
<td><strong>DSaO\textsubscript{2}, DSAT</strong></td>
<td>size of the change in arterial oxygen saturation ((\text{SaO}_2)) during a slow or quick oxygenation change.</td>
</tr>
<tr>
<td><strong>DtHb/DOI</strong></td>
<td>change of total haemoglobin ((\text{tHb})) with respect to the change in oxygen index during an oxygenation change.</td>
</tr>
<tr>
<td><strong>DUR</strong></td>
<td>duration of an oxygenation change.</td>
</tr>
<tr>
<td><strong>FiO\textsubscript{2}\textsuperscript{,}\textsuperscript{-}</strong></td>
<td>fraction of inspired oxygen ([%]), the concentration of oxygen in the inspired air.</td>
</tr>
<tr>
<td><strong>ga</strong></td>
<td>gestational age ([\text{weeks}]), the number of weeks between the last menstruation and birth. Term infants have a gestational age between 36 6/7 and 42 weeks.</td>
</tr>
<tr>
<td><strong>HHb</strong></td>
<td>deoxy-haemoglobin concentration per l of brain ([\text{μmol/l}]).</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>heart rate ([\text{beats/min}]) measured by the electrocardiograph.</td>
</tr>
</tbody>
</table>
**N** the number of measurements included in a statistical model.

**NIRS** near infrared spectrophotometry, a method to measure changes in HHb, O₄Hb and tHb in the brain.

**O₂Hb** oxyhaemoglobin concentration per l of brain [µmol/l].

**OC** oxygen consumption in ml per 100g of tissue (e.g. brain) per min [ml/(100g*min)].

**OE** oxygen extraction [%], equals to the difference between the arterial and venous oxygen saturation.

**OI** oxygen index [µmol/l] equals to half of the difference between O₂Hb and HHb.

**OO** oxygen offer [ml/(100g*min)], ml of oxygen offered to 100g of tissue per min.

**oxygen offer** see OO.

**oxygenation status** is a description of the state of tissue with respect to oxygen: How much oxygen is supplied (SaO₂, pO₂, cbv, cHbc, cbf, cHbf, tt, OO, cHb)? How much oxygen is consumed (SvO₂, OE, OC)?

**oxygen supply** corresponds to OO.

**pa** postnatal age [days]

**pCO₂** partial carbon dioxide pressure [kPa].

**pO₂** partial oxygen pressure [kPa].

**PR** pulse rate [beats/min] corresponds to HR, but is measured by the pulse oximeter.

**R²** correlation coefficient, indicates the quality of a linear fit. 1 refers to a perfect fit and 0 indicates no agreement.

**SaO₂** arterial oxygen saturation [%], the proportion of oxidised haemoglobin in the artery.

**SD** standard deviation

**SEM** standard error of the mean

**SH1, SH2** quality criteria referring to the amount of change, when a cerebral blood flow (cbf) measurement is calculated 1s respectively 2s later than the initial calculation.

**SOC** slow oxygenation change, a slow change in the oxygen concentration in tissue, which is induced by altering the amount of inspired oxygen (FIo₂).

**SOI** stability of the oxygen index (OI) before a quick oxygenation change.
SSAT stability of the arterial oxygen saturation (SaO₂) before a quick oxygenation change.

SSTHB stability of the total haemoglobin (tHb) during an oxygenation change.

SvO₂ venous oxygen saturation [%], the proportion of oxidised of all haemoglobin in the vein.

tHb total haemoglobin concentration per l of brain [μmol/l], corresponds to the sum of O₂Hb and HbB.

TRV test retest variability: the amount of variation encountered, when a measurement is repeated several times under the same conditions. It is a measure of the reproducibility of a method.

tt transit time [s], the time blood takes to pass an organ.

UCH one particular method to calculate cerebral blood flow (see chapter 5.3.1.)

Va corresponds to the TRV

Vr the variability between subjects.

ΔT sampling time [s]
3. Introduction

3.1. History of oxygen therapy

At the end of the last century it was discovered that preterm infants who had a blue complexion (cyanosis) quickly turned pink and healthy looking, when they were given oxygen to breathe [Lysel 1883, Duc 1995]. This was the beginning of a new epoch in the treatment of preterm infants, i.e. the oxygen therapy. It soon became a routine treatment, due to the beneficial effect of the oxygen administration on the survival rates [Hess 1934]. The culmination was in the 1940s, when it became customary to deliver oxygen concentrations of more than 50% for weeks in the breathing air.

In the middle of this century the first studies appeared, associating lesions of the eyes and even blindness with excessive oxygen supply [Patz 1952, 1954, Lanman 1954, Kinsey 1956]. This raised the question as to how much oxygen should be given to avoid lesions of the eyes on the one hand and an increased mortality on the other hand. To answer this question the means to assess the supply, concentration and consumption of oxygen, the oxygenation status of the newborn infant, had to be developed. Up to today this problem has not been solved satisfactorily.

3.2. The preterm infant and the neonatal clinic

To comprehend why an infant may need the special care of the neonatal clinic it is important to consider the enormous changes that the newborn infant experiences on being born [Micheli 1994]. Before birth the infant is in a warm, sterile, dark and quiet environment and in a buoyant state. It is supplied with nutrition and oxygen through the umbilical cord. A particularly interesting aspect is that the infant's development takes place although its oxygen supply is very low. The arterial partial oxygen pressure is 3.25kPa, which can be compared to the one one would have in the atmosphere atop the Mount Everest [Micheli 1994].

After birth the infant immediately has to regulate its temperature and oxygen supply on its own, despite the sudden exposure to room air with its much higher oxygen concentration compared to the mount Everest situation. The digestion and immune system have to start working on the
first day as well. The infant looses buoyancy and has to face other strong stimuli such as light and sound. Considering these enormous changes it is quite remarkable that most infants handle them without problems. However, especially preterm infants display problems to adapt to the new situation after birth. They are transferred to the neonatal clinic, where the intrauterine conditions are simulated until they are ready to cope with the world's environment.

To keep the infant warm, it is placed in an incubator, i.e. a box of Perspex with an air temperature which can be adjusted to the infant's needs. At the beginning the temperature will be around 37°. Then it is reduced slowly until it reaches normal room temperature. The humidity of the air is higher (typically 70%) compared to normal ambient conditions to prevent the infant from dehydrating. Furthermore the incubator shields against germs to prevent infections, which the preterm immune system may not be able to cope with.

It is important, that the Perspex of the incubator allows visual observation of the infant. For experienced staff one of the most important factors to judge the well being of the infant is the colour of the skin, e.g. a bluish colour indicates a lack of oxygen or a greyish colour is a sign of an infection.

As soon as possible the infant is fed with the milk of its mother. If the infant is not able to suck, the milk is transferred to the stomach by a feeding tube. In severe cases, nutrition can be given directly into the blood vessels.

The oxygenation can be supported in different ways. The concentration of oxygen in the inspired air can be increased. To prevent the lungs from collapsing a small tube is inserted into the nose, which exerts a continuous positive airway pressure (CPAP). If both of the mentioned interventions do not suffice, the infant is intubated, i.e. a tube is inserted in the trachea and mechanically ventilated.

In an intensive care unit the infants are kept under surveillance day and night by doctors, nurses and monitors, who check the vital functions like heart rate (electrocardiograph), blood pressure and oxygen concentration (pulse oximeter and partial oxygen pressure monitor) in the blood continuously. For all of the monitored parameters certain thresholds are fixed above or below which an alarm is triggered. Such an alarm indicates that the attention of a nurse is required. Yet, a nervous and moving infant will often trigger false alarms. Ultimately, this causes the staff to be less
attentive to this child, and in case of an apnea (i.e. a cessation of breathing), leave the infant hypoxic for an extended period of time. This is an every day problem in intensive care and is called the "crying wolf syndrome".

Figure 1: The environment in an intensive care unit. The infant is placed in an incubator. The monitors on the rack control the vital functions of the infant. To the right is a high frequency oscillator. A team of doctors and nurses cares for the infant day and night.
3.3. The pathological oxygenation status of the preterm newborn

Preterm infants often exhibit various problems with respect to the regulation of their oxygenation. Baeckert [1987] found that 56% of all hospitalised infants with a birthweight below 1500g developed a respiratory distress syndrome. Every organ can be affected by a lack of oxygen, which can be caused by any or a combination of the following factors:

1. The infant is too weak to maintain breathing sufficiently. It gets exhausted and therefore has to be mechanically ventilated.
2. The lungs are not fully developed, in particular, surfactant production may be insufficient or lacking altogether. Surfactant is an agent which
lessens the forces associated with surface tension in the alveolus. Due to a lack of surfactant the alveoli do not open properly during inspiration or collapse during expiration. This reduces the surface of the lung along with its gas exchange capacity. Consequently, the blood is less oxygenated. In such cases the preterm newborn can be treated with oxygen. The amount of oxygen given to the infant is called the fraction of inspired oxygen (FiO₂). As mentioned previously, to prevent the lungs from collapsing a small tube is inserted into the nose, which exerts a continuous positive airway pressure (CPAP). If both of the mentioned interventions do not suffice, the infant is intubated, i.e. a tube is inserted in the trachea and mechanically ventilated. Artificial surfactant is given to prevent the preterm lungs from collapsing.

3. Because of cerebral immaturity, the autoregulation of the oxygenation does not work properly. Resulting phenomena include periodic breathing, where the infant stops to breathe for up to 5s to 10s every 10 to 30 breaths, or apneas, where the infant suddenly stops to breathe altogether and may not resume breathing without intervention. These conditions require the surveillance of nurses and a monitoring equipment, which produces an alarm in such critical situations. Usually it is sufficient to stimulate the infant by stroking, brushing or shaking it slightly to reactivate its breathing.

4. An obstruction of the upper airways due to mucus or a relaxation of laryngeal muscles [Ruggins 1991] requires the intervention of a nurse.

5. An insufficient blood circulation fails to distribute the oxygenated blood to the whole body. Causes may be a persistent ductus arteriosus, a defect of the heart or a low blood pressure.

6. A deficit or malformation of the oxygen carrier (haemoglobin) reduces oxygen transport.

7. Local malperfusion due to impaired autoregulation [Volpe 1995] may affect a single organ, yet such a condition is difficult to diagnose, because this would involve the investigation of all organs separately. Not only a lack of oxygen is dangerous, but also too much oxygen due to excessive oxygen administration. This may cause for example damages to the eyes (retinopathy of the newborn [Körner 1984]). It also gives rise to the contraction of blood vessels, which can reduce blood flow for hours and thus may lead to a lack of oxygenation as well. Lundström [1995] found that if infants were given a high oxygen concentration during resuscitation right after birth, they had a lower cerebral blood flow even 2
hours after birth compared to a similar group with restricted oxygen. The reasons for this are not clear yet. All of these findings underline the need to carefully control the oxygen status of the ill newborn infant. This is particularly true for the organ which is the most sensitive concerning maloxygenation: the developing brain. It is essential to measure and control the oxygenation of the brain or other organs separately.

**3.4. The physiological parameters which determine the oxygen status**

Lesions of the brain are the most serious complication of the medical treatment of preterm infants. Therefore the focus in this thesis is on the brain. There are several parameters, which determine the oxygenation of the brain (figure 3) [Zander 1994].

![Circulatory model of the brain](image)

**Figure 3:** A circulatory model of the brain with the most important physiologic parameters for the oxygenation: OO = oxygen offer, cbf = cerebral blood flow, cHb = haemoglobin concentration in the blood, SaO₂ = arterial oxygen saturation, cbv = cerebral blood volume, cHbc = cerebral haemoglobin concentration, OC = oxygen consumption, OE = oxygen extraction, tt = transit time, SvO₂ = venous oxygen saturation.

1. The arterial oxygen concentration which denotes the amount of oxygen in the incoming blood. This is given by the arterial oxygen saturation (SaO₂ in %) or the partial oxygen pressure (pO₂ in kPa) and the haemoglobin concentration in the blood (cHb in mmol/l or g/100ml).
The relation between $\text{SaO}_2$ and $pO_2$ is unique, called the oxygen dissociation curve and shown in figure 4. There is a negligible amount of oxygen dissolved in the blood plasma. The maximum amount of oxygen that can be bound by 1g of haemoglobin, the Hufner number (H) corresponds to: $H = 1.39 \text{ ml O}_2/\text{g}$.

Figure 4: The oxygen dissociation curve shows the relationship between the partial oxygen pressure ($pO_2$) and the oxygen saturation ($SO_2$) of the blood. The physiologic arterial partial oxygen pressure ranges from 8kPa to 12kPa [Roberton 1986].

2. The oxygen concentration of the blood leaving the brain. In analogy to the arterial oxygen concentration, this is the venous oxygen saturation ($SvO_2$ in %) or partial oxygen pressure.

3. The cerebral blood flow (cbf in ml/(100g*min)), where the 100g refer to the mass of the brain which is being perfused. Related to this quantity is the time the blood takes to pass the brain, the so called transit time (tt in s). Both determine how often per unit of time the blood is exchanged in the brain. The brain of an infant with a body weight between 500g and 999g weighs on the average 109g [Hall 1989].

4. The cerebral haemoglobin concentration ($cHbc$ in $\mu\text{mol/l}$) is defined as $\mu\text{mol}$ of haemoglobin per l of brain tissue and denotes the concentration of haemoglobin per tissue. Using the cHb the cHbc can
be converted into the cerebral blood volume (cbv in ml/100g, i.e. ml of blood per 100g of brain), which is more common in the literature [Wyatt 1990]. For the oxygenation status, the cHbc is more important than the cbv, because it represents the concentration of the main oxygen carrier.

5. Although oxygen is converted into carbon dioxide (CO₂) in tissue, the partial carbon dioxide pressure (pCO₂), cannot serve as a measure of the oxygen consumption. The pCO₂ is influenced much more by other factors associated with metabolism and lung function. The number of breaths per unit time determines how much CO₂ is leaving the body, i.e. during hyperventilation the pCO₂ decreases. In general, this does not influence the pO₂, which can be regulated independently of the pCO₂.

For biochemical reasons the pCO₂ is inversely related to the pH of the blood, which reflects the acid-base status.

The most important parameters, which determine the oxygenation status, can be calculated according to the following equations taking into account the parameters introduced above:

\[
\text{Oxygen offer: } \quad OO = \text{cbf} \times \text{SaO₂} \times \text{cHb} \times \text{H} / 100 \quad \text{ml/(100g*min)}
\]

\[
\text{Oxygen extraction: } \quad OE = \text{SaO₂} - \text{SvO₂} \quad \%
\]

\[
\text{Oxygen consumption: } \quad OC = \text{cbf} \times \text{OE} \times \text{cHb} \times \text{H} / 100 \quad \text{ml/(100g*min)}
\]

The oxygen offer determines how much oxygen is being offered to the perfused tissue by the arterial side. The oxygen extraction is the difference between the arterial and the venous oxygen saturation. The oxygen consumption denotes how much oxygen is consumed per unit time by the tissue.

The cited parameters are interdependent. The most important relations are the following:

1. The mean transit time can be derived using the following equation:
   \[
   \text{Transit time: } \quad tt = 60 \times \text{cbv/cbf} \quad \text{s}
   \]

2. There is an inverse relation between cbf and SvO₂. In general, the lower the blood circulation, the more oxygen will be extracted from the blood.
3. cbv, cHbc and cbf are correlated linearly to pCO₂. An increase in pCO₂ causes an expansion of the blood vessels and hence an increase of the cbv. Due to the decreased resistance of the vascular bed, also cbf increases, unless there is a drop in blood pressure. These phenomena are attributed to autoregulation, which influences the tension of the muscles of the arterioles. It is unknown, how the pCO₂ is assessed by the body. One possible indicator may be the pH of the cerebro spinal fluid, which is inversely correlated to the pCO₂.

3.5. Technical state of the art to assess the oxygenation

The methods mentioned below are restricted to those which can be applied at the bedside. Under clinical conditions, it is very complicated to move intensive care patients, who are mechanically ventilated. This excludes the application of powerful methods like magnetic resonance imaging and spectroscopy, positron emission tomography, computer tomography etc.

A characteristic feature of the following monitors, which are used routinely to assess oxygenation, consists of the in-depth clinical experience which allows to define upper and lower limits for the measured values. Whenever the physiological range is not met, an alarm is produced:

- With the pulse oximeter a measurement is made which uses the light attenuation of tissue and of the blood contained in it, in particular, of oxy- and deoxyhaemoglobin, who exhibit markedly different absorption spectra. With every systolic pulse wave a certain amount of arterial blood is forced into the peripheral tissue due to the higher systolic pressure compared to the diastole. As the arterial blood concentration changes in the volume of the tissue irradiated by the pulse oximeter, the light attenuation undergoes characteristic variations along with it. Thus the pulsating part of the attenuation can be attributed to arterial blood. Furthermore, the attenuation is dependent on the wavelength. It can be shown that with light at two wavelengths the oxyhaemoglobin (O₂Hb) and deoxyhaemoglobin (HHb) components of arterial blood can be distinguished and quantified relative to each other. For a precise quantification the optical pathlength between emitter and detector has to be known. Nevertheless, using these two components, the arterial...
oxygen saturation (SaO₂) which corresponds to the amount of O₂Hb with respect the sum of O₂Hb and HHb, can be calculated.

\[
\text{Arterial oxygen saturation} \quad \text{SaO}_2 = \frac{\text{O}_2\text{Hb}}{\text{O}_2\text{Hb} + \text{HHb}} \quad (\%)
\]

The unknown factor referring to the optical pathlength would be the same in the numerator as well as the denominator and therefore cancels out.

Besides the arterial oxygen saturation the pulse rate, which corresponds to the heart rate, can be determined continuously by counting the number of pulsations per minute [Wyser 1994]. In adults the arterial oxygen saturation is measured on the fingertip or the earlobe, while in neonates the right hand or a foot is used. It is assumed, that the arterial oxygen saturation is the same in all arteries. This is not true under certain conditions such as a persistent ductus arteriosus, where venous blood with a low oxygen saturation is shunting from the lung artery directly into the aorta. A typical sign for this condition is, that the oxygen saturation at the left hand is lower than that at the right hand. Furthermore the central and peripheral oxygenation may deviate (e.g. in case of shock).

This technique is easy to apply, needs no calibration to each individual patient and measures one of the vital parameters. Unfortunately it is disturbed easily by movement. The amount of false alarms triggered due to movement is particularly high for the pulse oximeter.

- The **trancutaneous partial pressure monitor**, which measures arterial partial oxygen pressure (pO₂ in kPa) and partial carbon dioxide pressure (pCO₂ in kPa) through the skin. This method relies on the diffusion of these two gases through the skin. The gas concentrations are measured by ion-sensitive transducers. If the skin is heated, the small blood vessels widen and the measured gases can be attributed to arterial blood [Lübbers 1987]. This monitor is quite reliable. Due to the increasing thickness of the skin, pO₂ can, however, only be measured accurately in preterm infants during the first two to six weeks of life. Furthermore it is influenced by the blood circulation of the skin and the sensors have to be calibrated every eight hours and heated to 44°. Consequently the sensor has to be moved every four hours to prevent burns.
The pO\textsubscript{2} is again part of the vital information needed to assess the oxygenation status. However it has to be considered as a peripheral measurement as well.

As mentioned above the pCO\textsubscript{2}, is no measure of the oxygen consumption.

The transcutaneous partial pressure monitor is less susceptible to movements, however, the sensor has to be stuck to the skin in an airtight fashion and may leak or fall off. Depending on the local blood perfusion of the site of application, the partial pressure reading may be considerably too low or high. It therefore has to be regularly controlled by taking a blood sample. Furthermore, artefacts can be caused by applying pressure on the sensor, which reduces the blood perfusion. Nevertheless, the number of false alarms generated is low.

- The **electrocardiograph** measures the heart rate very reliably by analysing the electric signals generated by the heart activity. The heart rate is an important indicator for the blood circulation, but not for the cerebral oxygen status, because it is only indirectly related to blood flow in the different organs. This monitor causes no false alarms, unless the electrodes are ripped off by a moving infant.

- The **blood pressure monitor** measures the arterial blood pressure. During the first days of life, it is a routine procedure in ventilated neonates to measure the blood pressure invasively. The catheter can easily be inserted through the umbilical artery. Later on the blood pressure is measured non invasively with oscillometry. Blood pressure is an important physiological parameter, but is not an indicator of blood flow. The invasive blood pressure monitor is giving false alarms due to movement or changes in intrathoracal pressure, for instance due to crying.

There is a number of more recent techniques for use in monitoring vital parameters in intensive care. They are however not (yet) routinely applied, and, in particular, no physiological range is established, such that no alarm-producing limits are fixed.

- **Ultrasound Doppler** allows to determine the blood flow velocities in blood vessels. Blood flow depends on the cross-sectional area of a blood vessel and the mean velocity over this area. However, only the projection of the true velocity on the direction of the transmitted ultrasound beam is measured and therefore the measurement also depends on the angle between the incoming ultrasound signal and the
blood flow. Hence the measured blood flow velocity is not a simple indicator of blood flow [Anthony 1991]. Current efforts will be continued to overcome this problem [Moser 1992].

- **Xenon-133 clearance** is a method to determine the cerebral blood flow in adults and infants. From the course in time of the washout produced by either an injection or a few breaths of the radioactive Xenon-133 isotope, which is measured externally, a one compartment model of the human brain is fitted. It is not used routinely, because it is non continuous and radioactivity is used. However it assesses a vital parameter.

- **Invasive venous oximetry** uses an optical fibre, whose tip is usually placed in the right atrium of the heart to measure mixed venous oxygen saturation. The method implies that a mixture of the venous blood of the whole body is taken into account. This has become a standard practice in many adult intensive care units to assess the oxygen status of the whole body [White 1985]. In infants it cannot be used to judge the oxygenation of a particular organ and it strongly depends on where the tip of the fibre is put even within the atrium of the heart [Schulze 1995], because it cannot be assumed, that the venous blood is uniformly mixed in the atrium.

- **Laser Doppler** measures some averaged velocity of blood flow within the skin [Bonner 1981]. This may be taken as a measure of the perfusion of the skin. However the skin is not crucial in intensive care, moreover, the capillary network is anatomically quite irregular, such that the measurement cannot be interpreted in a straight forward fashion. The measurement is also disturbed by microvibrations of the tissue associated with physical tremor activity. Efforts to measure in deeper tissue are on the way [Hülser 1993].

- **Near infrared spectrophotometry** is a method, which makes use of the different light absorption of oxyhaemoglobin and deoxyhaemoglobin in the near infrared region to quantify their changes in concentration. The algorithm of near infrared spectrophotometry [Wray 1988] is based on the Lambert Beer law:

\[ A = \log_{10}( \frac{I_0}{I_t} ) = \alpha \cdot c \cdot L \]
where \( A \) is the attenuation in optical densities (OD), \( I_0 \) the light intensity incident on the medium, \( I_t \) the light intensity transmitted through the medium, \( \alpha \) is the specific extinction coefficient in \( 1/(mM*cm) \), \( c \) the concentration of the absorbing chromophore in mM and \( L \) the thickness of the medium in cm. This equation is however only true under conditions without scattering. If scattering is present, the equation has to be modified:

\[
A = \alpha * c * L * DPF + \text{const}
\]

Due to scattering, the distance the light is travelling in the medium is increased. This is accounted for by the differential pathlength factor (DPF), which indicates how many times longer the distance is. The DPF has been measured by several authors [Wyatt 1990, van der Zee 1992, Benaron 1995, Duncan 1995].

Another effect of scattering is, that not all of the emitted light hits the detector. The amount of light getting lost is assumed to be constant. This is only true, if scattering is high and the tissue remains geometrically stable.

According to this theory only changes in attenuation can be used for quantification, because the constant (const) is not known. In the near infrared band, changes of attenuation in tissue are mainly due to changes in blood circulation, because haemoglobin is a comparatively strong absorber. If oxyhaemoglobin (\( O_2\text{Hb} \)) and deoxyhaemoglobin (\( \text{HHb} \)), at least two different wavelengths will be needed. This yields the following system of equations:

\[
\begin{align*}
A_{\lambda,1} &= (\alpha_{\lambda,1}^{O_2\text{Hb}} * c_{O_2\text{Hb}} + \alpha_{\lambda,1}^{\text{HHb}} * c_{\text{HHb}}) * L * DPF + \text{const}_{\lambda,1} \\
A_{\lambda,2} &= (\alpha_{\lambda,2}^{O_2\text{Hb}} * c_{O_2\text{Hb}} + \alpha_{\lambda,2}^{\text{HHb}} * c_{\text{HHb}}) * L * DPF + \text{const}_{\lambda,2}
\end{align*}
\]

or using matrices and vectors:

\[
A = [\alpha] * [c] * L * DPF + \text{const}
\]

Only changes in attenuation are evaluated.

\[
\Delta A = [\alpha] * \Delta c * L * DPF
\]
Hence the change in concentration can be calculated from a change in attenuation:

$$\Delta c = \left[\alpha\right]^{-1} \frac{\Delta A}{(L \cdot DPF)}$$

In contrast to pulse oximetry, near infrared spectrophotometry actually quantifies changes of oxy- and deoxyhaemoglobin concentration. Furthermore, the output power of the light sources is higher allowing to penetrate more tissue than just the tip of a finger. It can readily be applied at the head of a newborn to investigate the changes in cerebral blood circulation.

### 3.6. Aim of this thesis

The aim of this thesis consists of presenting methods to determine the oxygenation status of newborn infants along with a strategy to provide a reliable alarm environment under clinical conditions. According to the discussion given in chapter 3.4 (see figure 3), the important factors to judge the oxygenation status of the neonate are the \(cHbc\), \(cHb\), \(cbv\), \(cbf\), \(tt\), \(SaO_2\), \(SvO_2\), \(OO\), \(OE\) and \(OC\). A minimum set of five independent quantities is \(cHb\), \(cHbc\), either \(cbf\) or \(tt\), \(SvO_2\) and \(SaO_2\). \(cHb\) is a trivial laboratory parameter, which is routinely determined from a blood sample. Near infrared spectrophotometry lends itself to determine the other four quantities and therefore provides a method to determine exhaustively the oxygenation status of the newborn infant. The various measurements are presented in steps. In particular, in chapter "4. How to Evaluate Slow Oxygenation Changes to Estimate Absolute Cerebral Haemoglobin Concentration by Near Infrared Spectrophotometry in Neonates" a method to assess \(cHbc\) by near infrared spectrophotometry is described. In a clinical environment the measurements are never ideal, i.e. certain fluctuations and noise, which may affect the physical assumptions of this method, are always present. To which degree these fluctuations affect the reliability of the method? To answer this question the \(cHbc\) measurements were repeated several times in clinically stable neonates and the test retest variability was calculated. The influence of fluctuations of different parameters on the test
retest variability was determined. The purpose of this study was to base this method on sound physical principles and to determine its reliability.

In "5. Optimising the Methodology of Calculating the Cerebral Blood Flow of Newborn Infants from Near Infrared Spectrophotometry Data" the methods to assess cbf by near infrared spectrophotometry are described. The procedure and purpose of this study was similar to the cHbc study.

One problem for the calculation of cbf was the unknown transit time in preterm neonates. In "6. Estimation of Cerebral Blood Volume and Transit Time in Neonates from Quick Oxygen Increases Measured by Near-Infrared Spectrophotometry" a one compartment model was implemented, which yields estimates for the transit time, cbv and cbf.

The SvO₂ is the biggest and most important problem [Dudell 1990]. Up to today it was measured either invasively (see 3.6) or with manoeuvres like tilting [Skov 1993] or jugular bulb occlusion. Tilting was only successful in 41% of the preterm infants. Jugular bulb occlusion is not very reliable [Colier 1995]. Both methods are complicated and only give results intermittently. A method to measure SvO₂ continuously was developed for this thesis as is described in "7. The Measurement of Cerebral Arterial and Venous Oxygen Saturation". In addition to the SvO₂ the method also yields a continuous SaO₂ signal. Hence the oxygen extraction can be measured continuously.

All of the methods are prone to produce artefacts mostly due to movements of the infant. Accordingly an excess amount of alarms is produced, which may lead to an unsatisfactory monitoring routine under clinical conditions. As a result of this "crying wolf syndrome", prolonged hypoxias may develop. In order to prevent hypoxias due to the crying wolf syndrome, Fuzzy Logic was applied to distinguish between critical situations and movement artefacts in "8. Improved Monitoring of Preterm Infants by Fuzzy Logic". Our Fuzzy system reduced the amount of alarms by a factor of eight without missing any critical situations.
4. How to Evaluate Slow Oxygenation Changes to Estimate Absolute Cerebral Haemoglobin Concentration by Near Infrared Spectrophotometry in Neonates

(Advances in Experimental Medicine and Biology, in press)

4.1. Abstract

The aim of this study was to find criteria to select valid slow oxygenation change (SOC) measurements by optimising the test retest variability (TRV) for two different methods to compute cerebral haemoglobin concentration (cHbc).

The cHbc is calculated from the slope of oxygen index (Ol) versus arterial oxygen saturation (SaO₂) during a SOC. The slope was determined by a linear regression (cHbcr) as well as by the ratio of the differences between the maximum and minimum values (cHbcm). 218 SOC measurements were obtained from 9 infants in 39 sessions by a Critikon Redox monitor 2001 and a Nellcor N-200 pulse oxymeter. The following criteria were calculated for each SOC: the duration (DUR), the changes of SaO₂ (DSaO₂), total haemoglobin (DtHb), mean arterial pressure (DMAP), carbon dioxide tension (DCO₂), total haemoglobin versus Ol (DTHB/OI) and for cHbcr the correlation coefficient (R²). The 75 lowest TRV of all combinations of criteria at various strictness were determined by a computer program.

As result, DUR, DSaO₂, DTHB/OI and R² proved to be useful selection criteria. cHbcr and cHbcm had a similar TRV (see table). The proposed criteria rejected about 50% of the measurements.

<table>
<thead>
<tr>
<th>METHOD</th>
<th>DUR</th>
<th>DSAT</th>
<th>DTHB/OI</th>
<th>R²</th>
<th>TRV</th>
<th>Mean cHbc</th>
</tr>
</thead>
<tbody>
<tr>
<td>cHbcr</td>
<td>&gt;1.2 min</td>
<td>&gt;4%</td>
<td>&lt;25% and &gt;-25%</td>
<td>&gt;0.85</td>
<td>17.3%</td>
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<tr>
<td>cHbcm</td>
<td>&gt;1.5 min</td>
<td>&gt;4%</td>
<td>&lt;25% and &gt;-25%</td>
<td></td>
<td>18.3%</td>
<td>38.7 μmol/l</td>
</tr>
</tbody>
</table>

In conclusion an acceptable TRV is achieved by these criteria. The simpler cHbcm method is almost as precise as the cHbcr method.
4.2. Introduction

Brain injury is a major cause of long-term disability in newborn infants. Disturbed cerebral haemodynamics and oxygen supply may be important etiological factors, and these are currently investigated. Near infrared spectrophotometry (NIRS) in combination with pulse oxymetry is widely used to determine cerebral blood volume (cbv) in neonates. In a similar, but simpler way cerebral haemoglobin concentration (cHbc), which is more relevant for cerebral oxygenation, can be obtained from the same measurements. It is better to use the cHbc instead of the cbv because:

The haemoglobin content in blood does not have to be measured by drawing blood from the infant.

Furthermore we do not have to rely on a factor to convert the arterial or venous haemoglobin content into a capillary content.

We do not have to assume the haematocrit to be constant during a monitoring session.

The concentration of the oxygen carrier per tissue, the haemoglobin, is more important for the tissue oxygenation than the blood volume, which has been used in papers so far, because blood volume may be high, when haematocrit is low. Especially in newborn infants there is a wide variance of haemoglobin content in blood.

Under clinical conditions measurements are sometimes disturbed. The aim of this study was to find criteria to select valid slow oxygenation changes (SOC) measurements by optimising the test retest variability (TRV) for two different methods to compute cHbc.

4.3. Theory

The principle of NIRS has been described extensively by Jobsis (1977), Wray (1988) and von Siebenthal (1992). NIRS measures quantitatively changes in oxygenated haemoglobin (O₂Hb in \( \mu \text{mol/l} \)), deoxygenated haemoglobin (HHb in \( \mu \text{mol/l} \)) and total haemoglobin (tHb in \( \mu \text{mol/l} \)) concentrations in the brain.

The measurement principle for cerebral blood volume was first described by Wyatt (1986 and 1990). A SOC is induced by altering the inspired oxygen fraction (FiO₂) of infants, who need additional oxygen. During this change the arterial oxygen saturation (SaO₂ in %) is measured by pulse
oxymetry together with $O_2$Hb, HHb, tHb by NIRS. The SaO$_2$ is kept in a normal range between 85% and 95% (Figure 1).

![Graph showing changes in SaO2, O2Hb, HHb, and tHb over time.](image)

Figure 1: shows a typical slow oxygenation change. Arterial oxygen saturation (SaO$_2$) and oxyhaemoglobin ($O_2$Hb) are decreasing and deoxyhaemoglobin (HHb) is increasing simultaneously during an alteration of FiO$_2$. The total haemoglobin (tHb), which corresponds to the sum of $O_2$Hb an HHb, is supposed to remain constant. Obviously the tHb shows some small changes. Do these changes affect the validity of the measurements?
Figure 2: shows an X-Y plot of the first 5.5 min of Figure 1. Arterial oxygen saturation (SaO₂) and oxyhaemoglobin O₂Hb correlate more or less linearly.

The slope between O₂Hb and SaO₂ (Figure 2) is determined by a linear regression. The slope gives the amount of additional O₂Hb per % change in SaO₂. The cHbc corresponds to the amount of additional O₂Hb for an extrapolated total (100%) change in SaO₂ (equation 1).

\[
(1) \quad \text{cHbc} = 100 \times \frac{d\text{O}_2\text{Hb}}{d\text{SaO}_2} \left( \frac{\text{[\mu mol]}\text{[l]}}{} \right)
\]

Assuming that tHb remains constant during the SOC, the HHb must react equal but opposite to the O₂Hb. Hence the signal to noise ratio can be improved by taking the oxygen index (OI) instead of O₂Hb (equation 2).

\[
(2) \quad \text{OI} = \frac{\text{O}_2\text{Hb} - \text{HHb}}{2} \left( \frac{\text{[\mu mol]}\text{[l]}}{} \right)
\]

The estimate of the slope can be further improved by applying two regressions, one using SaO₂ as abscissa and OI as ordinate and the other vice versa. Then the bisector of the angle between the two slopes is taken (equation 3). The noisier the data the further the two slopes are apart.
cHbcr in equation 3 includes both improvements mentioned above. It is the first method to evaluate SOC.

Therefore the simple method cHbcm (equation 4), which just uses the minimum and maximum values of SaO₂ (SaO₂max, SaO₂min) and the synchronous OI values (Olmax, Olmin) to calculate the slope, was tested as well. cHbcm can easily be estimated with a pocket calculator looking at a good graph.

Equations 3 and 4 are true under the following assumptions: a) The tHb remains constant during the SOC. b) The amount of oxygen consumed is constant. c) The SOC is slow enough, such that the cerebral oxygenation remains in steady state. d) There is a linear correlation between Ol and SaO₂.

A SOC is never ideal with respect to these 4 assumptions, e.g.: the change in tHb during an SOC is never absolutely zero. What amount of change is still acceptable? To answer this question, quality criteria were defined, which quantify the change. Their influence on the TRV indicates how much change is acceptable.

4.4. Data collection

4.4.1. Test-retest procedure

In clinically stable infants consecutive changes in FiO₂ produced SOC. The prerequisite for a true TRV is, that the actual cHbc remains constant for all estimates during a session, which corresponds to one group of repeated measurements. This was considered to be fulfilled, if the total haemoglobin concentration (tHb) did not vary by more than ±1.5μmol/l during a session.
4.4.2. Equipment

For the cerebral parameters a Critikon Cerebral RedOx Research Monitor 2001 was used. The differential pathlength factor for the quantification of the NIRS data was 4.4. Either a Hellige SMK 231 or a Nellcor N-200 pulse oxymeter measured the SaO$_2$ at the right hand of the infant. The data was recorded with a 0.56s sample interval.

4.4.3. Patients

Nine infants, which were either mechanically ventilated or had a nasal CPAP and needed additional oxygen, were included in this study. The infants had a median gestational age of 27 2/7 weeks (range: 26 1/7 weeks - 29 2/7 weeks), birthweight of 1030g (750g - 1290g) and postnatal age of 0.5 days (0 days - 8 days). 218 SOC measurements were recorded during 39 sessions. The sessions contained 3 to 12 SOC.

4.5. Data processing

By averaging 18 samples the data were converted to an approximate 10s sample interval. cHbcr and cHbcm were calculated for all 218 SOC.
Figure 3: shows, how the quality criteria were defined for the first 6 minutes of Figure 1. DUR corresponds to the duration of the slow oxygenation change. DOI refers to the change in oxygen index, DtHb to the change in total haemoglobin and DSaO₂ to the change of arterial oxygen saturation during that time.

4.5.1. Quality criteria

As possible selection criteria the following variables were calculated for each SOC (Figure 3): The duration (DUR), the changes of SaO₂ (DSaO₂), tHb (DtHb), mean arterial blood pressure (DMAP), carbon dioxide (DCO₂), DtHb versus DOI (DtHb/DOI) during the SOC and the correlation coefficient (R², only for the regression).

4.5.2. Statistics

The chHbcr and chHbcm values were log-transformed to obtain homogeneity of variance. The TRV was determined according to equation
5. The total number of measurements has to be considerably higher than the number of sessions.

\[
TRV = \sqrt{\frac{\sum_{i=1}^{p} \sum_{v=1}^{n_i} (y_{iv} - \bar{y}_i)^2}{N - p - y_{..}}}
\]

\(n_i\) = Number of measurements in the ith session
\(p\) = number of sessions
\(N\) = total number of measurements
\(y_{iv}\) = vth measurement in the ith session
\(\bar{y}_i\) = mean of the ith session
\(y_{..}\) = global mean

The 75 lowest TRV of all possible 16000 combinations of the quality criteria at various levels of strictness were determined by a computer program. Because the TRV depends on the number of degrees of freedom remaining, after the acceptable measurements were selected, the program returned the lowest TRV for different minimum numbers of degrees of freedom.

4.6. Results

<table>
<thead>
<tr>
<th>Method</th>
<th>DUR</th>
<th>DSaO₂</th>
<th>DtHb/DOI</th>
<th>(R^2)</th>
<th>TRV</th>
<th>Mean cHbc</th>
</tr>
</thead>
<tbody>
<tr>
<td>cHbcr</td>
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<td></td>
<td>18.3%</td>
<td>38.7μmol/l</td>
</tr>
</tbody>
</table>

Table 1 shows the optimal quality criteria. Both cHbcr and cHbcm are given for tetrameric haemoglobin.

DUR, DSaO₂, DtHb/DOI and \(R^2\) were found to be useful selection criteria (Table 1). cHbcr and cHbcm had a similar TRV (Table 1). The proposed criteria rejected about 50% of the measurements.
Table 2 shows how many measurements were rejected by each criterion.

### 4.7. Discussion

The solutions shown in Table 1 were chosen out of the 75 returned by the computer program according to three considerations: the optimum TRV, the lowest number of SOC rejected and the reproducibility. A lower TRV of 13% can be achieved by using stricter quality criteria and hence rejecting 75% of the SOC (e.g. by increasing $R^2 > 0.96$ for $cHbcr$ in Table 1). If only 25% of the SOC are rejected, the TRV will increase to 23%. A reasonable balance between low TRV and high rejection was found in the solutions of Table 1. The most important criteria to reduce the TRV were $DtHb/DOI$ and $R^2$. DUR and D$SaO_2$ were not critical for the TRV of our data, probably because most of our SOC were above a crucial limit. Nevertheless they were given in Table 1, because they may become important for somebody trying to reproduce our data with lower DUR and D$SaO_2$.

DUR and D$SaO_2$ may be influenced by the operator during the measurement. These numbers in Table 2 could therefore be reduced.

The assumptions identified in the "theory" section are discussed below:

a) $tHb$ is measured continuously and it therefore does not have to be assumed to be stable. In practice it shows, that $tHb$ is never absolutely stable and this poses the question of how much change of $tHb$ is acceptable? The change of $tHb$ is set in relation to the change in $O_1$ during the SOC, which corresponds to quality criterion $DtHb/DOI$, because the bigger the change in $O_1$ the less an instability of $tHb$ matters. This proved to be the best criterion among the ones pertaining to $tHb$ ($DtHb$, D$CO_2$ and DMAP).

b) All changes in $SaO_2$ are small and in a normal range, i.e. the brain is well oxygenated. Hence it is unlikely, that a change in $SaO_2$ affects the oxygen consumption of the brain. Furthermore a change in cerebral oxygen metabolism will disturb the linear relationship between $SaO_2$ and...
Ol, which is taken into account by $R^2$. Still small changes may not be totally excluded and may constitute part of the TRV.
c) That a change is slow enough is accounted for by DUR.
d) Movement artefacts may play a role during measurements. Again they are likely to affect the linear relation between $\text{SaO}_2$ and Ol, which is controlled by $R^2$.
Part of the TRV in the range of 18% may be explained by the small resolution of the pulse oxymeter of 1%.
Wyatt (1990) obtained a mean cbv value of 2.22±0.40 (SD) ml/100g for healthy infants. For comparison we converted our cHbcr and cHbcm values into cbv and obtained 2.48±0.85 ml/100g respectively 2.33±0.78 ml/100g. Although the median gestational age and birthweight of our infants was lower by 1 5/7 weeks respectively 470g, our cbv is in good agreement with Wyatt (1990).

4.8. Conclusions

A set of quantitative criteria determines the quality of the SOC measurement. A TRV of 17.3% respectively 18.3% can be achieved, if approximately 50% of the measurements are discarded. The cHbcm method, which is much simpler to calculate, is almost as precise as the cHbcr method.
5. Optimising the Methodology of Calculating the Cerebral Blood Flow of Newborn Infants from Near Infrared Spectrophotometry Data

(Medical & Biological Engineering & Computing, May 1996)

5.1. Abstract

Cerebral blood flow can be measured in neonates by near infrared spectrophotometry. The tracer is oxyhaemoglobin. The first purpose of this study was to compare the test retest variability of two previously proposed methods of analysis and to investigate the influence of sampling rates, smoothing and integration periods. Under clinical conditions good measurements were often difficult to obtain. Therefore the second goal was to find ways of distinguishing the quality of individual measurements. 380 cerebral blood flow measurements from 69 infants were analysed. The data set was optimised statistically for the lowest test retest variability and the following results were obtained: 1) The test retest variability of measurements at 2s sampling time data was considerably worse than at 0.5s sampling time, 2) smoothing did not change the test retest variability, 3) a 6s integration period gives higher values and higher test retest variability than an 8s integration period. Applying the suggested criteria a test retest variability of 17% was achieved, if 50% of the measurements were rejected. The mean cerebral blood flow was 12.2 ml/(100g*min) for the one method and 9.7 ml/(100g*min) for the other method. The test retest variability of both methods is comparable for 0.5s sampling time. For 2s sampling time the method proposed by Skov (1991) is significantly better. These test retest variabilities represent maximum values, part of the observed variability may be due to physiological changes of unknown magnitude.
5.2. Introduction

Hypoxic-ischaemic brain injury is a major cause of long-term disability in newborn infants. Impaired cerebral blood flow (cbf) may be an important etiological factor. Several quantitative methods to measure cbf are available for neonates: venous occlusion plethysmography, 133-labelled Xenon clearance technique, positron emission tomography and near infrared spectrophotometry (NIRS). NIRS is non radioactive and can be applied repeatedly at the cotside. However, the data obtained from NIRS are analysed in different ways (Skov 1991; Bucher 1993). Under clinical conditions good measurements were often difficult to obtain. Quality criteria for the selection of appropriate measurements have been proposed by Skov (1991) but not evaluated. Therefore the aims of this study were to:

1. Find the method of analysis with the best test retest variability.
2. Evaluate criteria to judge the quality of individual NIRS measurements.
3. Quantify the systematic difference between the various methods.

5.3. Theory

The principle of NIRS has been described extensively by Jobsis (1977), Wray (1988) and von Siebenthal (1992). NIRS measures quantitatively changes in oxygenated haemoglobin ($O_2Hb$ in mmol/l) and deoxygenated haemoglobin ($HHb$ in mmol/l) concentrations in the brain. The Fick principle is applied to measure the cbf taking $O_2Hb$ as tracer. It states that the rate of accumulation ($Q$) of a tracer in an organ is equal to the difference between its arterial ($Ca$) and venous ($Cv$) concentration multiplied by the blood flow ($F$) (equation 1).

$$\frac{dQ}{dt} = F \times (C_a - C_v) \quad (1)$$

The left side of equation 1 ($dQ/dt$) can be measured by NIRS. $Ca$ is determined by a pulse oximeter (arterial saturation: $SaO_2$ in %) in combination with the arterial haemoglobin concentration ($cHb$ in mmol/l). If there is a change in $Ca$ e.g. by giving a bolus of oxygen after a steady
state (Figure 1), it will take several seconds - the so-called transit time—until it reaches the venous compartment and $C_v$ is affected. If the calculations of flow are based only on the data obtained before the transit time has elapsed, it is not necessary to know $C_v$ (equation 2).

\[
\text{cbf} = \frac{Q}{cHb} \int C_a dt = \frac{\Delta O_2 Hb}{cHb} \int \Delta SaO_2 dt = \frac{5.71 \times (O_2 Hb(t) - O_2 Hb(t_0))}{cHb} \int_{t_0}^{t_1} \Delta SaO_2 dt \frac{ml}{100g \times \text{min}}
\]

Figure 1: An example for an induced rapid increase in oxygen, which is followed by a more gradual increase of the cerebral oxygen index

The scaling factor 5.71 evolves from the conversions of 1l to 100g of brain (density 1.05g/ml) and time from seconds to minutes (dt is in seconds). $t_0$ was defined to be the last point in steady state, preceding four consecutive increasing values. $t_1$ occurs some seconds later - at any time before the transit time has elapsed.

The cerebral blood volume expressed as the total cerebral haemoglobin concentration ($tHb$), which corresponds to the sum of $O_2 Hb$ and $HHb$, is assumed to be constant during the oxygenation change. Hence $HHb$ is decreased by the same amount as $O_2 Hb$ is increased. The oxygen index
(OI) (equation 3), gives a better signal to noise ratio and is less biased by changes in tHb (equation 4).

\[
OI = \frac{O_2Hb - HHb}{2} \mu mol / l \tag{3}
\]

\[
cbf = \frac{5.71 \times (OI(t_1) - OI(t_0))}{cHb \times \int_{t_0}^{t_1} \Delta SaO2 * dt} \text{ ml / (100g*min)} \tag{4}
\]

The measurements provide non-continuous data with sampling times (Δt) of 0.5s or 2s. Therefore the integral is replaced with a sum (equation 5).

\[
cbf = \frac{5.71 \times (OI(t_1 + \DeltaEL) - OI(t_0 + \DeltaEL))}{cHb \times \sum_{t_0}^{t_1} \Delta SaO2 * \Delta t} \text{ ml / (100g*min)} \tag{5}
\]

DEL accounts for the small time shift of OI compared to SaO2, which occurs, because SaO2 is not measured in the brain. Although this equation is simple, two considerably different methods of analysis have evolved. It is the first goal of this study to find out, which method has a lower test retest variability.

5.3.1. UCH-method (Proposed by Edwards (1988))

10s of SaO2 just before the increase are averaged to get the steady state (AVGSAT). To replace the sum of SaO2 the trapezoidal rule is used. A straight line of one integration period length (\(t_{int}\) equation 6) is fitted (least square fit) into all stages of the OI increase. The highest slope found among these lines (\(DOImax\)) is used for the calculation of cbf (equation 7).

\[
t_{int} = t_1 - t_0 \tag{6}
\]

This eliminates the problem of determining DEL for the OI increase. However, the noisier the data the more \(DOImax\) and cbf will be overestimated. Theoretically the OI curve is proportional to the integral of SaO2, if cbf and cHb are constant. For a clear step in SaO2 the increase in
OI should be linear. In reality $SaO_2$ increases linearly (Figure 1) and the OI increase should therefore correspond to a parabola and not to a straight line.

\[(7)\]

\[
\text{cbf} = \frac{5.71 \times \Delta OImax \times t_{\text{int}}}{cHb \times (\sum_{t=0}^{t-1} (0.5 \times SaO_2(t) + 0.5 \times SaO_2(t + 1) - AVGSAT) \times \Delta t)} \text{ ml} \]

\[
5.3.2. \text{ COP-method (Proposed by Skov (1991))}\]

This method (equation 8) applies a polynomial fit (4th order for 0.5s and 2nd order for 2s sample time for 10s) to smooth the period of increase of $OI$ and $SaO_2$.

To find the steady state conditions, the 10s before the increase are averaged (AVGSAT, AVGOI).

\[(8)\]

\[
\text{cbf} = \frac{5.71 \times OI(t_1 + \text{DEL}) - AVGOI}{cHb \times (\sum_{t=0}^{t_1} (SaO_2(t) - AVGSAT) \times \Delta t)} \text{ ml} / (100g \times \text{min})
\]

The point of increase of $SaO_2$ or OI is determined by a computer program looking for 4 consecutively increased samples. This point can be corrected manually.

The simple sum (COP) will always give higher values for the integral of $SaO_2$ compared to the trapezoidal rule (UCH) and hence systematically smaller cbf.

**5.4. Methods**

**5.4.1. Data collection**

**5.4.1.1. Test-retest procedure**

Changes in OI were produced by increasing the inspired oxygen concentration to 100% for 10s. This was done repeatedly to test the variability within a session; a session being defined as a period in which a group of OI increases were induced and cbf could be assumed stable -
i.e. no change in treatment and monitoring of transcutaneous partial carbon dioxide pressure as well as mean arterial blood pressure showed only minimal changes (up to 0.2kPa respectively 3mmHg).

5.4.1.2. Equipment

The neonatal unit in Zurich used a Hamamatsu NIR 1000 to measure the cerebral parameters and a Nellcor 200 pulse oximeter for the \( \text{SaO}_2 \). The Hamamatsu NIR 1000 has 6 wavelengths and a photon counter allowing to penetrate 8cm of tissue. The highest sample rate achievable was 1 Hz. The Nellcor pulse oximeter averages for 2s. For this study the data was recorded with 2s sample time.

In Copenhagen a Radiometer NIRS device and a Datex pulse oximeter were applied. The Radiometer instrument has four wavelengths and an avalanche diode as receiver. The pulse oximeter renders beat to beat saturation values. The data was recorded with 0.5s sample time. The pulse oximeter sensors were fixed whenever possible on the right hand and otherwise on the left hand.

5.4.1.3. Patients

Sixty nine infants of the neonatal units of Copenhagen (24) and Zurich (45) were included in this study. They were all mechanically ventilated and required additional oxygen. The infants were clinically stable. The infants, who were measured at 0.5s sampling rates, had a gestational age of median 30 weeks (range: 25-42 weeks), postnatal age of 4 days (1-44 days) and a birthweight of 1465 g (820-4050 g). 117 measurements were available.

The infants with 2s sampling rates, had a gestational age of median 28 weeks (range: 25-42 weeks), postnatal age of 5 days (1-118 days) and a birthweight of 1010 g (580-4050 g). 380 measurements were available. The measurements needed a minimal \( \text{SaO}_2 \) increase of 2% within the first 8s to be included.

5.4.2. Data processing

Both the COP- and the UCH-method were used on \( t_{\text{int}}=6s \), \( t_{\text{int}}=8s \) and on smoothed as well as unsmoothed data (smoothing algorithm: equation 9).
\[ Y_{\text{smoothed}}(t) = 0.1^* Y(t - 2) + 0.2^* Y(t - 1) + 0.4^* Y(t) + 0.2^* Y(t + 1) + 0.1^* Y(t + 2) \]

To get a higher number of measurements, all 0.5s samples were additionally converted to 2s samples by averaging 4 samples.

### 5.4.2.1. Quality criteria

The second goal of this study was to find criteria to judge the quality of each measurement, whether the increase was big enough, the steady state conditions fulfilled according to the Fick's principle and the baby quiet.

![Quality criteria graph](image)

Figure 2: Quality criteria shown for an increase in saturation. There are two different sorts of quality criteria: The actual increase = DSAT, and the stability=(B-A)/DSAT, which is normed to DSAT, because an instability is the less important the bigger the increase.

Fig. 2 shows the intervals of relevance for the application of quality criteria on the SaO₂ transient. The actual increase after 8s corresponds to DSAT.
(in %). To get a measure of the quality of the steady state (SSAT in %), we took an average over period A (20s to 14s before the increase) and B (6s to 0s) and normed their difference to DSAT, because a stable steady state matters more if DSAT is low (equation 10).

\[
SSAT = \frac{B - A}{DSAT} \%
\]

The stability of OI before the increase (SOI in %) and change in OI after 8s (DOI in mmol/l) are calculated analogously to SSAT and DSAT respectively. DOI, however, is meaningless, because it depends directly on the cbf.

The stability of tHb (STHB) is determined by norming the change of tHb (DTHB) during the 8s period to DOI, again because a steady tHb is more important if DOI is small (equation 11).

\[
STHB = \frac{DTHB}{DOI} \%
\]

Another quality criterion is the delay (DEL) between the SaO2- and the OI-increase.

Finally the whole cbf-calculation was repeated for t0+1s (only for 0.5s sampling time) and t0+2s. Then we calculated the SH1 and SH2 (in %) as possible indicators of stability (equations 12 and 13). SH1 and SH2 were determined for the UCH as well as the COP method.

\[
SH1 = \frac{cbf(t_0 + 1s) - cbf(t_0)}{cbf(t_0)} \%
\]

\[
SH2 = \frac{cbf(t_0 + 2s) - cbf(t_0)}{cbf(t_0)} \%
\]

5.4.3. Statistics

All values for cbf were log-transformed to obtain homogeneity of variance, because of positive skewness.

A session is a period of maximum 2 hours during which several cbf measurements are carried out on the same infant. It was assumed, that
during the same session the cbf does not change. Two components of variance: The *intra* component ($\sigma^2_i$) is the variance within the sessions and the *inter* component ($\sigma^2_r$) indicates the variance between the sessions (equations 14 and 15).

$$\sigma^2_i = \frac{\sum_{i=1}^{p} \left( \frac{\sum_{v=1}^{n_i} (y_{iv} - y.)^2}{n_i} \right) - \frac{\sum_{i=1}^{p} \sum_{v=1}^{n_i} (y_{iv} - y.)^2}{N - p}}{N - \frac{\sum_{i=1}^{p} n_i^2}{N}}$$

$$\sigma^2_r = \frac{\sum_{i=1}^{p} \sum_{v=1}^{n_i} (y_{iv} - y.)^2}{N - p}$$

(14)  \quad (15)

$$\text{Va} = \frac{\sigma^2_i}{y.}$$

$$\text{Vr} = \frac{\sigma^2_r}{y.}$$

(16)  \quad (17)

$n_i$ = Number of measurements in the $i$th session  
$p$ = number of sessions  
$N$ = total number of measurements  
$y_{iv}$ = $v$th measurement in the $i$th session  
$y_i.$ = mean of $i$th session  
$y.$ = global mean

$\text{Va}$ and $\text{Vr}$ (in %) correspond to the coefficients of variance (equations 16 and 17). The method yielding the smallest $\text{Va}$ has the lowest test retest variability. The relation between $\text{Va}$ and $\text{Vr}$ reflects the amount of test retest variability compared to the variability between sessions. Residuals, i.e. the differences of individual measurements to the mean of their session, were calculated for sessions containing at least 3 measurements. The residuals were plotted against the various quality criteria. High residuals can be associated with quality criteria above or below a certain level. For each criterion four levels were set, which the cbf
measurements would have to fulfil to be acceptable. The following ranges were used for the individual quality criteria (absolute values): DEL 1s to 11s; minimal DSAT 2.5% to 4.5%; maximal DSAT 6% to 11%; SSAT 20% to 80%; SOI 20% to 80%; STHB 40% to 160%; SH1 15% to 50%; SH2 20% to 120%. To determine which combination of which quality criteria at what particular level would yield the smallest Va, a computer program was written to test all of the approximately 700000 combinations. Because Va depends on the number of degrees of freedom remaining, after the acceptable measurements were selected, the program returned the lowest Va for different minimum numbers of degrees of freedom. The solutions in Table 1 and 2 were tested for susceptibility to small changes in quality criteria. Only stable solutions were accepted.

Bland and Altman (1986) proposed to compare two measures by plotting their geometric mean versus their quotient. This type of plot allows to judge the difference between the UCH- and the COP-method. The logarithmic scales are used to get homogeneity of variance (Fig. 3 to 6).

5.5. Results

5.5.1. Integration period of 8s and unsmoothed data

There is a linear correlation between the Va and the number of degrees of freedom. This means that stricter quality criteria will reduce Va. It is therefore quite difficult to choose an optimum solution. Two solutions are shown in Tables 1 and 2.
<table>
<thead>
<tr>
<th>ΔT</th>
<th>DEL</th>
<th>DSAT</th>
<th>SSAT</th>
<th>SOI</th>
<th>STHB</th>
<th>SH1</th>
<th>SH2</th>
<th>Mean cbf</th>
<th>Va</th>
<th>Vr</th>
<th>N</th>
<th>DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>s</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>ml/100g*min</td>
<td>%</td>
<td>%</td>
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<td></td>
</tr>
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<td>0.5</td>
<td>≤8</td>
<td>≥3 to ≤8</td>
<td>≤70</td>
<td>≤80</td>
<td>≤80</td>
<td>≤25</td>
<td>≤40</td>
<td>9.7</td>
<td>19</td>
<td>55</td>
<td>60(117)</td>
<td>31</td>
</tr>
<tr>
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<td>≥3</td>
<td>≤70</td>
<td>≤70</td>
<td>≤80</td>
<td>≤25</td>
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<td>50</td>
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<td>79</td>
</tr>
<tr>
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<td>≤11</td>
<td>≥3 to ≤11</td>
<td>≤60</td>
<td>≤50</td>
<td>≤100</td>
<td>≤50</td>
<td>10.8</td>
<td>29</td>
<td>64</td>
<td>154(380)</td>
<td>75</td>
<td></td>
</tr>
<tr>
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<td>≤11</td>
<td>≥3</td>
<td>≤80</td>
<td>≤80</td>
<td>≤160</td>
<td>≤90</td>
<td>12</td>
<td>40</td>
<td>62</td>
<td>250(380)</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.2</td>
<td>55</td>
<td>54</td>
<td>380(380)</td>
<td>259</td>
</tr>
</tbody>
</table>

Table 1: The solutions for various strictnesses of selections for the COP-method. Exceptionally for the 2s sampling time data the results given are for smoothed data, because smoothing improves the Va by about 5%. ΔT=sample time, DEL=delay, DSAT=saturation increase after 8s, SSAT=stability of the saturation before the increase compared to DSAT, SOI=stability of the cerebral oxygen index before the increase, STHB=stability of cerebral total haemoglobin volume during the increase, SH1,SH2=divergence of an analysis 1s respectively 2s later, Mean cbf=mean cerebral blood flow, Va=test retest variability, Vr=coefficient of variance in between infants, i.e. compared to Mean cbf, N=number of measurements remaining in the data set (original number), DF=degrees of freedom.
The UCH-method and 0.5s sampling time data offer a better Va than the COP-method and 2s sampling time data. However the better Va for the UCH method is due to the higher average of cbf. An F-test comparing \( \sigma_a \) of samples with similar N reveals that \( \sigma_a \) of the COP method is always smaller, but only statistically significantly (\( \alpha \leq 5\% \)) smaller for 2s sampling time.

There is a remarkable difference between the average flow of 0.5 and 2s sample time measurements. This may be explained by the longer sampling period of the pulse oximeter in Zurich, where the 2s sample time data was recorded, causing an underestimation of the saturation integral.

Table 2: The solutions for various strictnesses of selections for the UCH-method.

<table>
<thead>
<tr>
<th>( \Delta T )</th>
<th>DEL</th>
<th>DSAT</th>
<th>SSAT</th>
<th>SOI</th>
<th>STHB</th>
<th>SH1</th>
<th>SH2</th>
<th>MEAN cbf</th>
<th>Va</th>
<th>Vr</th>
<th>N</th>
<th>DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>s</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>ml/100g*min</td>
<td>%</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 ≤7,5</td>
<td>≥3</td>
<td>≤30</td>
<td>≤80</td>
<td>≤60</td>
<td>≤30</td>
<td>≤30</td>
<td>12,2</td>
<td>17</td>
<td>56</td>
<td>59(117)</td>
<td>30</td>
<td></td>
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<tr>
<td>0.5 ≤8</td>
<td>≥3</td>
<td>≤30</td>
<td>≤60</td>
<td>≤120</td>
<td>≤30</td>
<td></td>
<td>11,3</td>
<td>23</td>
<td>59</td>
<td>70(117)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td>46</td>
<td>51</td>
<td>117(117)</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>2 ≤7</td>
<td>≥3 to ≤9</td>
<td>≤80</td>
<td>≤80</td>
<td>≤80</td>
<td>≤16</td>
<td>24,5</td>
<td>33</td>
<td>71</td>
<td>206(380)</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 ≤9</td>
<td>≥3 to ≤9</td>
<td>≤80</td>
<td>≤80</td>
<td>≤140</td>
<td>≤16</td>
<td>23,8</td>
<td>38</td>
<td>72</td>
<td>225(380)</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22,7</td>
<td>53</td>
<td>72</td>
<td>380(380)</td>
<td>259</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.5.2. Comparison between UCH- and COP-method

The UCH-method renders higher values than the COP-method (Fig. 3 and 4).

Figure 3: Plot according to Bland and Altman, 1986 for the comparison of 0.5s sampling rate cerebral blood flow values calculated according to the UCH and the COP method. The UCH method returns bigger values.
Figure 4: Plot (Bland and Altman, 1986) for the comparison of 2s sampling rate cerebral blood flow values calculated according to the UCH and the COP method. The UCH method returns bigger values.
5.5.3. 6s integration period

The longer the integration period the more the noise is averaged out. Taking only the first 6s as integration period, increases the Va by 25% to 35% compared to the 8s integration period. This is true for all the above described methods and sampling times except for 2s sample time according to the UCH-method, which has a three times bigger Va. As previously observed (Skov 1991), in Figure 5 the COP-method (0.5s sampling time) gives significantly higher results for flows above 20 ml/(100g*min) when using a 6s integration period. This is due to the transit time being less than 8s at high flow rates. In addition to this error the UCH-method shows higher values for a 6s integration period throughout the whole range of cbf values (Fig. 6). This can be explained by the relatively higher noise level at 6s.

![Graph](image)

Figure 5: Plot (Bland and Altman, 1986) for the comparison of cerebral blood flow values calculated according to the COP method using 6s (COP6) and 8s (COP8) as integration period. The reason for higher results according to COP6 in the high flow region is probably that the transit time was shorter than 8s, which would result in underestimation of cerebral blood flow according to COP8.
Figure 6: Plot (Bland and Altman, 1986) for the comparison of cerebral blood flow values calculated according to the UCH method using 6s (UCH6) and 8s (UCH8) as integration period. The mean cerebral blood flow is generally higher for UCH6. The reason for unproportionally high results according to UCH6 in the high flow region is probably that the transit time was shorter than 8s, which would result in underestimation of cerebral blood flow according to UCH8.

5.5.4. Smoothing

Smoothing the SaO₂ and OI before processing leaves Va and the average flow virtually unchanged. Only for the COP-method in 2s sampling time the Va is improved by a few percent. If the saturation or the OI is smoothed, the average flow is increased or decreased respectively. Hence both variables should be smoothed, if at all.

5.5.5. Steady state condition

Several methods to determine the steady state before the increase were tested. It proved to be best to take an average of the 10s preceding the increase.
5.5.6. Influence of repeated measurements on the flow

In the same session the difference of one flow measurement to the previous one was taken. Only those measurements were taken into account, which were less than 3 minutes apart. The mean difference for COP was: (mean ± 95% confidence interval) -1.57 ± 3.39 ml/(100g*min) and for UCH: -1.18 ± 6.17 ml/(100g*min) and hence statistically not different from zero. Due to the large confidence interval, an influence cannot be excluded.

5.6. Discussion

The sources of error may be divided into three groups: violations of the Fick principle (physiology), technical errors of measurement and statistical errors.

5.6.1. Violations of the Fick principle

The tracer should be inert and should not disappear from the measured compartments. Additional oxygen should not result in increased oxygen consumption and should not influence cerebral blood volume or flow as long as the infants are adequately oxygenated (SaO₂ above 85%) (Brun 1994).

Transit time is inversely related to cbf. Hence in infants with a high flow the minimal transit time may be below 8s. Arnot (1970) suggest a mean transit time of 6.6s to 10s in term neonates. However, neither mean nor minimal transit time in preterm infants are known. Fig. 5 and 6 suggest, that for cbf above 20 ml/(100g*min) an integration period of 6s should be used. This issue needs further consideration.

5.6.2. Technical errors

NIRS measurements are susceptible to movement artefacts, which are very unlikely to interfere with short measurements of 20s. For accurate measurements by NIRS the optical path length has to be known and remain constant. While it is not yet possible to measure it
directly, for our study it was assumed to be 4.4 (± 0.28) times the interoptode distance (Wyatt 1990). Most recent measurements by van der Zee 1992 on babies post mortem suggest a value of 3.85 (± 0.57). The standard deviation does not change Va, but it adds an artefact to Vr.

The resolution of the pulse oximeter read-out is only 1%. This results in a theoretical maximum error of 33% assuming a DSAT of 3% and worst case for a single measurement. Realistic assumptions lead to an average contribution to the Va of less than 5%.

In Zurich the pulse oximeter gave 2s averaged saturation data. Both the NIRS and the pulse oximeter data were recorded with a sampling time of 2s, which may cause step increases to be smoothed. This results in an average additional Va of approximately 11%.

In Copenhagen the pulse oximeter yielded beat to beat values and all of the data was sampled with 0.5s sampling rates, which reduces the average additional Va to around 2.5%.

Va represents a maximum estimate of the imprecision of the method. cbf may vary somewhat even though the infant is clinically stable. The magnitude of short-term variability of cbf in newborn infants is unknown. Doppler monitoring suggests, that it may be up to 12% (Anthony 1991).

5.6.3. Statistical errors

This was an exploratory study. Therefore it cannot be excluded, that new data will have a bigger Va. There were not enough degrees of freedom to do a confirmatory study. To minimise the influence of random only stable solutions with at least 30 degrees of freedom were accepted.

The values of cbf as well as Va are reasonable and in agreement with the previous studies and Xenon clearance method (Skov 1991; Bucher 1993). In the study by Skov 1991 cbf determined by the COP-method was slightly lower than by the Xenon clearance method. In the study by Bucher 1993 the UCH-method yielded higher cbf values than by Xenon clearance. This difference can now be explained quantitatively by the systematic difference between the UCH- and the COP-method (Fig. 3 and 4).

Va can be reduced by averaging n measurements. The reduced Va corresponds to the original Va divided by the squareroot of n.
5.7. Conclusion

UCH and COP were found to have a comparable test retest variability. With either method it was only possible to achieve a test retest variability better than 20% by discarding 50% of the measurements. These test retest variabilities represent maximum values, because it cannot be excluded, that part of them is due to physiological changes.

A set of quantitative criteria describes the quality of the cbf measurements.

The UCH method yields significantly higher values compared to COP. The test retest variability of measurements at 2s sampling rates data is considerably worse than at 0.5s sampling rates. Smoothing does not improve the test retest variability. 6s integration period gives higher values and poorer test retest variability than 8s integration period.
6. Estimation of Cerebral Blood Volume and Transit Time in Neonates from Quick Oxygen Increases Measured by Near-Infrared Spectrophotometry

(Advances in Experimental Medicine and Biology, 1996, 93-100)

6.1. Abstract

Quick oxygen increases are used to estimate the cerebral blood flow (cbf) in neonates by near infrared spectrophotometry. The Fick principle is applied for this purpose. One of the essential assumptions for the correct estimation of cbf is, that the transit time (tt) exceeds 6s to 8s. A simple one compartment model is applied to estimate the tt. If the mean tt is known, the suggested one compartment model will also supply estimates for the cerebral blood volume (cbv).

82 measurements were obtained from nine infants. The mean tt was 17.60 (SD = 4.36) s, the cbf 6.98 (3.48) ml/(100g*min), the cHbf 1.00 (0.42) g/(100g*min), the cbv 1.82 (0.71) ml/100g and the cHbw 0.28 (0.09) g/100g.

The simple mathematical model gives reasonable results for cerebral blood and haemoglobin flow, blood volume, haemoglobin weight and transit time.

6.2. Introduction

Quick oxygen increases are used to estimate the cerebral blood flow (cbf) or cerebral haemoglobin flow (cHbf) in neonates by near infrared spectrophotometry (NIRS) (Edwards 1988 and 1993, Skov 1991, Bucher 1993). One of the essential assumptions for the correct estimation of cbf by the Fick principle is, that the time a bolus of tracer needs to pass the cerebral compartment - the so-called transit time (tt) - exceeds 6s to 8s. This paper describes a way of estimating the tt.

If the mean tt is known, the suggested one compartment model will also supply estimates for the cerebral blood volume (cbv) or the cerebral haemoglobin weight (cHbw).

6.3. Theory
Figure 1: The one compartment model. The arterial oxygen saturation (\(\text{SaO}_2\)) is measured by a pulse oximeter and the cerebral oxygen index (OI) is measured by near-infrared spectrophotometry (NIRS). This allows to calculate the cerebral blood flow (cbf), the transit time (tt) and the cerebral blood volume (cbv).

For the analysis a one compartment model is applied (Fig. 1). The following assumptions are made:
1) The oxygen saturation (\(\text{SaO}_2\)) of the haemoglobin and the haemoglobin concentration of the blood flowing into the brain are known.
2) The brain corresponds to one compartment. In this compartment all of the blood takes the same time tt to flow through.
3) NIRS measures the global changes in cerebral oxygenated haemoglobin (\(\text{O}_2\text{Hb}\)) and deoxygenated haemoglobin (HHb).
4) The brain is well oxygenated before each measurement (\(\text{SaO}_2>85\%\)). Giving additional oxygen does not change the cerebral oxygen consumption, which is unknown. Only the additional oxygen is taken into account for all the following calculations.

The \(\text{SaO}_2\) is adjusted to a lower normal level (aim 90%) and should be in a steady state for about one minute. A step increase in oxygen is given. These measurements are restricted to ventilated infants needing additional oxygen.

Fig. 2 shows a typical measurement with an increase in \(\text{SaO}_2\) followed by an increase in the oxygen index (OI), which equals to \(\text{OI} = (\text{O}_2\text{Hb} - \text{HHb}) / \text{cbf}\)
\( \text{HHb}/2 \). \( \text{O}_2 \text{Hb} \) gives a better signal to noise ratio than \( \text{O}_2 \text{Hb} \) as long as the total haemoglobin volume (tHb) remains the same during the measurement.

\[
\text{cbf}(ip) = k \frac{\Delta \text{O}_2 \text{Hb}(ip)}{cHb \int_0^t \text{SaO}_2 \cdot dt}
\]

For the calculation of cbf as a function of the integration period (ip), equation 1 is applied to a quick increase in oxygen. \( k \) is a conversion constant and \( cHb \) corresponds to the haemoglobin content in arterial blood.

\[
\text{cbf}(ip) \cdot cHb \cdot \int_0^t \text{SaO}_2 \cdot dt
\]

\[
\text{Olsim}(t,ip) = -t \frac{\text{cbf}(ip) \cdot cHb \cdot \int_0^t \text{SaO}_2 \cdot dt}{k}
\]

Knowing cbf, Olsim can be simulated as a function of time (t) and ip (equation 2). The slope of Olsim during the time of the oxygen increase correlates inversely to ip (Fig. 3). The ip, where the slope of Olsim corresponds best to the slope of Olsim is determined numerically by minimising the mean square distance between the Olsim - and the measured \( \text{O}_2 \text{Hb} \) curve. It is equal to this ip.
Figure 2: A typical example of a quick oxygen increase. A rapid increase of arterial oxygen saturation (SaO₂) is followed by a slower increase of oxygen index (Oi).

(3) \[ cHbf(ip) = k \frac{\Delta OI(ip)}{\int_0^t SaO_2 \, dt} \]

(4) \[ Olsim(t, ip) = \frac{cHbf(ip) \int_0^t SaO_2 \, dt}{k} \]

By an analogue procedure, it is possible to determine the cHbf (equations 3 and 4).
Assuming a one compartment model \( cbv = rt \ast cbf \) or \( chbw = rt \ast cHbf \).
Figure 3: Comparison of simulated oxygen index (Olsim) curves for different integration periods (10s, 20s, 30s, 40s, 50s, 60s) to the measured oxygen index (Ol) curve. The longer the integration period the flatter is the slope of the Olsim curve. The curve with 30s integration period corresponds best to the actual measurement.

6.4. Material and methods

Eighty-two measurements were obtained from nine mechanically ventilated babies, who needed additional oxygen. A Nellcor N-200 pulse oximeter in beat to beat or 2s sampling time mode was used to measure the SaO₂. The changes in O₂-Hb and HHb were recorded by a Critikon Cerebral Oxygenation Monitor 205 at a sampling time of 0.57s.
6.5. Results

The detailed results are in Table 1. The mean tt was 17.60 (SD = 4.36) s, the cbf 6.98 (3.48) ml/(100g*min), the cHbf 1.00 (0.42) g/(100g*min), the cbv 1.82 (0.71) ml/100g and the cHbw 0.28 (0.09) g/100g.

<table>
<thead>
<tr>
<th>ga</th>
<th>bw</th>
<th>pa</th>
<th>N</th>
<th>tt</th>
<th>cbf</th>
<th>cHbf</th>
<th>cbv</th>
<th>cHbw</th>
<th>clinical condition</th>
</tr>
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<tbody>
<tr>
<td>26(0/7)</td>
<td>980</td>
<td>19</td>
<td>5</td>
<td>16.6 (1.8)</td>
<td>5.9 (0.5)</td>
<td>0.7 (0.06)</td>
<td>1.59 (0.15)</td>
<td>0.20 (0.02)</td>
<td>severe hmd</td>
</tr>
<tr>
<td>26(1/7)</td>
<td>980</td>
<td>3</td>
<td>10</td>
<td>14.4 (1.0)</td>
<td>15.1 (2.3)</td>
<td>2.1 (0.31)</td>
<td>3.44 (0.38)</td>
<td>0.48 (0.06)</td>
<td>severe hmd</td>
</tr>
<tr>
<td>27(5/7)</td>
<td>1020</td>
<td>0</td>
<td>12</td>
<td>20.0 (1.4)</td>
<td>4.0 (0.3)</td>
<td>0.8 (0.06)</td>
<td>1.30 (0.12)</td>
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<td>1160</td>
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<td>16</td>
<td>21.5 (2.5)</td>
<td>5.2 (0.8)</td>
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<td>0.25 (0.03)</td>
<td>severe hmd</td>
</tr>
<tr>
<td>28(3/7)</td>
<td>920</td>
<td>7</td>
<td>7</td>
<td>13.6 (1.9)</td>
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<td>7</td>
<td>15.0 (3.3)</td>
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<td>1</td>
<td>3</td>
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<td>3.7 (1.3)</td>
<td>0.5 (0.22)</td>
<td>1.36 (0.40)</td>
<td>0.21 (0.04)</td>
<td>diaphragm. hernia, severe asphyxia</td>
</tr>
</tbody>
</table>

Table 1: The results of the calculations. The values in this table are given in: Mean (SEM) ga = gestational age in weeks, bw = birthweight in g, pa = postnatal age in days, N = Number of measurements, tt = transit time in s, cbf = cerebral blood flow in ml/(100g*min), cHbf = cerebral haemoglobin flow in g/(100g*min), cbv = cerebral blood volume in ml/100g, cHbw = cerebral haemoglobin weight in g/100g, hmd = hyaline membrane disease.
Figure 4: The mean transit times of the nine infants versus the gestational age. In addition the values measured by Arnot 1970 are shown.

Figure 5: The cerebral blood flow versus the gestational age.
Figure 6: The cerebral haemoglobin flow versus the gestational age

Figure 7: The cerebral blood volume versus the gestational age
Figure 8: The cerebral haemoglobin weight versus the gestational age

6.6. Discussion

Pulse oximetry may be a source of considerable error. Most pulse oximeters only have a resolution of 1% in \( \text{SaO}_2 \) and 2s in time, because of filtering. The pulse oximeter we used was specially adapted to for this study, i.e. the filtering was turned off. This produced a higher time resolution (one value per heart beat) with a resolution of 0.1% with an improved dynamic (step response). In return the noise level was higher. According to [Lammertsma 1988] the haemoglobin content in the blood (cHb) may vary depending on the diameter of the vessel. Therefore it is more reliable and physiologically more relevant to give cHbf and cHbw instead of cbf and cbv. In this paper cbf and cbv are only used to compare the values to the ones previously published.

Considering the blood circulation, the head of the newborn infant contains three compartments: grey matter, white matter and skin. From the \( ^{133}\text{Xenon} \) clearance method it is known, that the grey matter compartment is very small in neonates (10%) and has a very high flow (8 to 10 times higher than white matter), so that the transit time must be very small (around 1s to 3s) [Jaeggi private communication]. On the one hand the time resolution (0.56s) of the current measuring equipment is not good enough to get stable estimates. On the other hand such a small
compartment can be neglected. The skin compartment is small and has a low blood flow. Therefore it can be neglected as well. This is in accordance with the routine use of the 133Xenon clearance in neonates, which applies a one compartment model as well [Bucher, 1993]. The principles of NIRS have been discussed extensively by Cope 1988. Our results for tt are higher than those reported by Arnot 1970, who found values between 6.6s and 10s in 5 patients with gestational age between 42 and 36 weeks. The difference can be explained by the lower gestational age of our infants except for the two infants with a gestational age above 35 weeks. These two infants were both severely ill (Table 1). It is impossible to get healthy infants at this age, which are intubated. Our remaining tt fit well into the extrapolation of the values of Arnot 1970. The values for cbf are in the lower range of previous publications (Edwards 1988 and 1993, Skov 1991, Bucher 1993). They used shorter ip between 6s to 8s, which result in higher estimates. The ip used for the calculation of cbf in this paper equals to the tt, which is only correct under the strict assumption, that all the blood takes the same time to pass the compartment. What ip should be taken? There are two effects: 1. Due to the grey matter compartment, the cbf estimates decrease with increasing integration period. 2. If some of the additionally oxygenated blood leaves the brain before the ip is elapsed, this results in underestimation of the cbf. The advantages of choosing an ip in relation to the tt would be, that a maximum ip can be adjusted individually to each infant, which will give less noisy results and reduce the influence of effect 1. To avoid effect 2 the ip must be shorter than the tt. Therefore we suggest to use an ip, which is around 70% of the tt. This issue needs further consideration. Our values for cbv are in the lower range of the 2.22 (SD 0.40) ml/100g published by Wyatt 1990, that are also based on near-infrared spectrophotometry (NIRS), but analysed in a different way.

6.7. Conclusion

We report a simple mathematical model using NIRS data, which gives reasonable results for cerebral blood and haemoglobin flow, blood volume, haemoglobin weight and transit time. Further studies are needed to show its accuracy and clinical value.
7. The Measurement of Cerebral Arterial and Venous Oxygen Saturation

7.1. Abstract

Up to today the continuous measurement of venous oxygen saturation had to rely on invasive techniques like catheters or non-continuous procedures such as tilting or jugular bulb occlusion. The physiologic basis for the measurement of cerebral venous oxygen saturation was found in the observation that venous blood pressure exhibits characteristic changes which have to be attributed to mechanical ventilation. To measure the arterial oxygen saturation synchronously to the venous oxygen saturation, newly developed pulse oximetric techniques were used. For the detection of both pulsating signals, a photometer with high time resolution was built with sufficient power to penetrate up to 3.5cm of tissue. The signals from the heads of 15 ventilated neonates were retrieved, filtered and converted to venous and arterial oxyhaemoglobin and deoxyhaemoglobin concentration changes. The first clinical results indicate a mean arterial oxygen saturation of 89.9% (SD 5.4%) and a mean venous oxygen saturation of 73.0% (SD 11.7%).

7.2. Physiologic basis

7.2.1. Physiology during spontaneous breathing

The physiological effects of spontaneous breathing on the blood circulation in the brain have been described by Elwell [1994]. The pressure in the thorax is positive during expiration and negative during inspiration. Accordingly, during inspiration the intrathoracal pressure falls. This drop is transmitted via the thin walls of the right ventricle to the whole venous circulation, such that the venous return increases along with the amount of blood entering the pulmonary circulation. The in relation to the right ventricle thicker wall of the left ventricle leaves the arterial side virtually unaffected. In contrast the blood flow to the left ventricle is even inhibited due to the pooling of blood in the lung, which is again caused by the negative pressure.
During expiration this blood is squeezed out of the lung into the left ventricle, which causes a rise in cardiac output. Due to all of these interactions it is very difficult to attribute changes in peripheral blood concentration caused by breathing to the arterial or venous compartment.

7.2.2. Physiology during mechanical ventilation

During mechanical ventilation the physiological effects on the blood circulation in the brain are much simpler. The pressure in the thorax is always positive to keep the lungs inflated. During "inspiration" the ventilator exerts a higher pressure and during "expiration" the pressure is released to a predetermined positive value ("positive pressure ventilation"). During the period of higher pressure, the return of venous blood is inhibited. This effect can be made visible by our spectrophotometer with high time resolution described in chapter 7.3 (figure 1).

In this study, the described physiological reaction induced by mechanical ventilation was used to determine the $SvO_2$ from the systematic variations observed in the venous return.

With every heart beat a certain amount of arterial blood is forced into tissue due to the higher systolic pressure compared to the diastole. As the arterial blood concentration changes in the volume of the tissue irradiated, the light attenuation undergoes characteristic variations, which can be used to measure the $SaO_2$. 
Figure 1: The raw signal corresponds to the light attenuation obtained by placing an emitter and detector 2.5cm apart on the front of a ventilated infant's head. The three curves represent: 1. The raw attenuation data without filtering, which consists of two overlaid pulsations, one from the heart rate and one from the ventilation rate. 2. The data, where the heart rate was filtered out by a band pass. For both of these attenuation curves, the baseline is arbitrary. 3. The schematic curve of the ventilator pressure in bar, which was divided by a factor of 10 for a more convenient graphic.

7.3. Spectrophotometer with high time resolution

7.3.1. Requirements for a spectrophotometer with high time resolution

The main purpose of this photometer is to detect signals of the brain with a sufficient time resolution to measure attenuation changes due to heart beats and ventilator pressure changes.

The light has to penetrate the skull and the skin. The mean skull thickness at the frontal ossification centre is 0.40mm (SD 0.10mm) [Ohtsuki 1977] for a term newborn infant and is more transparent than an adult skull. The thickness of the skin is in the same range as the one of the skull and
depends on the pressure exerted by the sensor. It is estimated, that the light has to penetrate less than 3mm of tissue until it reaches the brain and again on the way back to the sensor. To get a signal from the brain and its main vein, the sinus sagittalis, the emitter detector distance has to be more than 6mm, the more the better.

Figure 2: This schematic diagram shows the frontal section of the head. The light from the emitter has to penetrate the three layers skin, skull and cerebro spinal fluid (csf), which have a total thickness of less than 3mm in neonates, before it reaches the brain. The light also passes the sinus sagittalis, the vein, which collects the venous blood from the brain. The amount of light reaching the detector mainly depends on the brain and the sinus sagittalis, while the influence of the three layers is small.

The light absorption of the skull and skin is considerable in adults. It was shown, that cerebral blood flow measurements by near infrared spectrophotometry were 69% lower on the average, if the detectors were attached on the head (emitter detector spacing 4.2cm) compared to the situation, where emitter and detector where placed directly on the brain [Owen-Reece 1996]. The reasonable agreement of cerebral blood flow measurements by near infrared spectrophotometry compared to the 133-
xenon clearance method in neonates [Skov 1991, Bucher 1993] suggest, that the contribution of skull and skin in the neonate is small and may be neglected. Therefore, for the use in neonates the emitter detector distance does not have to be as large as in adults. A distance above 2cm is sufficient, but a longer distance is desirable. The Critikon 2001 cerebral redox research monitor uses a fixed distance of 3.5cm. Therefore the photometer beam should be able to penetrate 3.5cm of tissue.

In normal human tissue the loss of light is about 1OD/cm or, in other words, the light intensity is weakened by a factor of 10 per cm. Near infrared spectrophotometers available today only have a time resolution of 0.5s. To detect the two pulse waves of the heart and the ventilator, a sampling rate of at least 15Hz (-10dB energy spectrum) is needed, because the heart rate in preterm infants can be up to 190beats/min, which equals 3Hz with components of up to 30 Hz (-20dB). To be able to measure up to three substances (oxyhaemoglobin, deoxyhaemoglobin and a dye like indocyanine green) the photometer needs at least three different wavelengths (see chapter 7.4.1.).

7.3.2. Hardware implementation

In a previous thesis a three-wavelengths pulse oximeter was implemented as a slot card for a personal computer with an ISA-bus [Wyser 1994]. This open design allowed a great latitude for experimentation, as it was favourable for testing of various algorithms and tissues. It was adapted for the new photometer used in this study. Thereby, the digital part was reused, while the analogue part, the sensor and the software had to be redesigned.
7.3.3. Measurement procedure

The emitter and detector are fixed to the tissue to be examined. At first the amplifiers are calibrated to zero. Then the output power of each LED is adjusted to the optical characteristics of the tissue, such that none of the receiving amplifiers gets into non-linear or saturated regions. During this procedure the amplification may be adjusted as well.

All of the signals are pulsed in order to distinguish between the different wavelengths. In a sample and hold circuit the signals of each wavelength and the ambient light are collected separately. The ambient light is then subtracted from the LED signals. A hardware low pass filter of 15 Hz is applied to smooth the signal. The signal is then converted into a digital signal by the AD converter.

The digital values are transferred to the PC, where the signals are analysed further and the SaO₂ as well as the SvO₂ is calculated.

The function and hardware implementation of each block is discussed in the following section.
7.3.4. Sensor

There are three LEDs of each wavelength arranged on as little space as possible. Thus three times more light is emitted and a better signal to noise ratio is achieved.

Figure 4: Schematic diagram of the light emitter with nine LEDs, three for each wavelength and the detector with a PIN diode, which is shielded against noise.

The sensor has to be flexible with respect to emitter-detector spacing. Hence the emitter and detector were implemented separately with each a cable of 80cm length. Both cables end in a preamplifier box. The preamplifier ensures low noise detection. The material in which detector and emitter are wrapped in as well as the cable shields have to be medical grade nonalergenic. Any sharp edges or points were smoothed. The sensor can be disinfected before use. The preamplifier box is not sterile and has to be placed outside the incubator.
7.3.5. Light sources

There are basically 3 possible light sources:

1. Bulbs with a continuous spectrum using a monochromator. The advantage of such a system is, that a continuous spectrum is available. The disadvantages are, that a bulb cannot be put into the sensor and that a broad spectrum requires more power for an adequate light intensity at the desired wavelength than a light source with a small suitably chosen spectrum, which would be sufficient for this purpose and due to this the light may warm up the tissue.

2. LED’s have a narrower spectrum. They are cheap, easy to handle, may be put into a sensor and do not harm the eyes or skin. The disadvantage of LEDs is the still quite broad bandwidth (40nm).

3. Lasers have a very narrow bandwidth. There are various types of Lasers, but for this purpose the best is the Laser diode. Unfortunately it is very expensive to get the required wavelengths today due to a shielded market. Furthermore they cannot be put into the sensor, because they have to be temperature controlled. A fibre optic is needed to carry the light to the skin. Most important, the light of laser diodes is potentially harmful when focused, especially to the eye, which requires special safety devices.

The main disadvantage of the LED, the wider bandwidth, can be accounted for in the algorithm. The output power of LEDs is lower than of laser diodes, but still sufficient for our purpose.

The LEDs used for the sensor are specially developed for medical purposes. They have a particularly low bandwidth (20nm) compared to normal LEDs, are powerful and built for SMD technology, which means they are physically small. Thus three LEDs of each wavelength were put into the emitter, still yielding a small and light emitter.

There is a sufficient range of wavelengths available of the LEDs used. Thus the wavelengths can easily be adapted for the detection of other substances such as dyes like indocyanine green.
7.3.6. Detector

There are again three general forms of detectors:

1. The photoncounter is very sensitive, is too large to be mounted to the sensor and is expensive. The major drawback is its limited input power range, which requires that during in vivo measurements the site of measurement has to be carefully shielded against ambient light. This is particularly difficult in an intensive care unit, where infrared lamps are used to keep the patients warm.

2. The avalanche diode is quite sensitive, reasonably expensive, but needs a high voltage (typically 400V) and hence is difficult to put into a sensor.

3. The silicon photodiodes have a linear behaviour, are easy to handle, small and can be put directly into the sensor. This reduces losses of light compared to a fibre optic. For our purposes this detector has a sufficient input sensitivity. It also has a wide input power range and therefore allows to deal with ambient light without shielding.
Figure 6: The sensitivity profile of the applied PIN photodiode.

The PIN photodiode used for our purpose is very light and flat. It was covered by a copper grid to shield against electromagnetic interference evolving from the monitoring equipment in the intensive care unit.

7.3.7. DA converter

This 12bit converter allows the programming of the output power of the LEDs, which can be adjusted in 4096 steps. The drivers for the LEDs had to be implemented separately, because their output power has to be adjusted to the tissue characteristics individually (figure 7). This is always done at the beginning of a new measurement.
Figure 7: The three emitting LEDs are pulsed successively with a short interval to detect the amount of ambient light (shaded area).

7.3.8. Drivers

The signal from the DA converter is then multiplexed and reaches a MOSFET driver, which is carefully shielded against high voltages evolving from the inductivity of the long cables (5m).

7.3.9. Preamplifier

To avoid interference, the preamplifier is put as close as possible to the patient. The preamplifier circuit converts the current from the PIN photodiode into a voltage. The output of the photodiode and preamplifier has a signal to noise ratio between 40dB and 60dB and a high light
sensitivity to detect a light signal of a few µW. Because of the limited space in the intensive care unit a 4m long cable following the preamplifier is necessary. The cable is shielded against electromagnetic interference.

7.3.10. Sample and Hold

The incoming signals are fed through a programmable amplifier, which allows to adjust an amplification between 25 and 123 times. The three pulsed wavelengths, which are time multiplexed in the signal from the preamplifier are separated in the sample hold section. As can be seen in figure 8, there are four states, which are continuously repeated: During the first three states one of the wavelengths is emitted and in the fourth state, the ambient light is detected. The evolving four signals are then low pass filtered (cut-off: 15Hz) and the ambient light is subtracted from the three LED channels. This subtraction is indispensable in a clinical environment, where light shielding is impractical.

The signals are once more amplified, before they reach the AD converter.
Figure 8: The pulses for the sample and hold circuit are shorter than the ones from emitting diodes. The 3 wavelengths and ambient light are separated in time.
7.3.11. AD converter

A 12Bit AD converter is used to get sufficient resolution. The input range is 10V. The three LEDs as well as the ambient light channels are converted. The ambient light has to be controlled to prevent the amplifiers from getting saturated. The data is then buffered in a FIFO and transferred to the PC.

7.3.12. Patient safety

For the electrical safety of the patients, the photometer has to be electrically separated from the mains. The whole PC was therefore connected to a 1:1 isolation transformer, which has a dielectric strength of more than 5000V.

7.3.13. Noise reduction

In an intensive care unit there are a lot of sources of electromagnetic interference like cathode ray tubes. For that reason there are several noise reductions implemented. The first important step is a good shielding of all exposed parts. The circuit has to have short signal paths. The use of LEDs allows longer pulses of light compared to laser diodes. Therefore their stability can be better controlled. A least square fit algorithm can be applied due to the use of three instead of two LEDs. In the receiving circuit filters help to eliminate the noise, because the sampling rate is higher than actually needed.

7.4. Algorithm

7.4.1. Theory

There are several approaches to convert the measured light attenuations to chromophore concentrations:

a) The empirical approach uses a phantom with similar light scattering like in tissue and adds different amounts of blood with known oxygen saturation. This empirical calibration curve is used as a look up
table, where the optical data is inserted. This is common in pulse oximetry.

b) The theoretical approach, which is used in near infrared spectrophotometry [Wray 1988] is based on the Lambert Beer law:

\[ A = \log_{10}\left( \frac{I_0}{I_T} \right) = \alpha \cdot c \cdot L \]

where \( A \) is the attenuation in optical densities (OD), \( I_0 \) the light intensity incident on the medium, \( I_T \) the light intensity transmitted through the medium, \( \alpha \) is the specific extinction coefficient in \( 1/(\text{mM} \cdot \text{cm}) \), \( c \) the concentration of the absorbing chromophore in mM and \( L \) the thickness of the medium in cm. This equation is however only true under conditions without scattering. If scattering is present, the equation has to be modified:

\[ A = \alpha \cdot c \cdot L \cdot \text{DPF} + \text{const} \]

Due to scattering, the distance the light is travelling in the medium is increased. This is accounted for by the differential pathlength factor (DPF), which indicates how many times longer the distance is. The DPF has been measured by several authors either by an intensity modulated system [Benaron 1995, Duncan 1995] or by direct time of flight measurements with a picosecond laser pulse and a streak camera [Wyatt 1990, van der Zee 1992]. It is known for various tissues [Colier 1995]. Another effect of scattering is, that not all of the emitted light hits the detector. The amount of light getting lost is assumed to be constant. This is only true, if scattering is high and the tissue remains geometrically stable.

According to this theory only changes in attenuation can be used for quantification, because the constant (const) is not known. In the near infrared band, changes of attenuation in tissue are mainly due to changes in blood circulation, because haemoglobin is a comparatively strong absorber. Some tissue components like e.g. bone have a constant attenuation with respect to time.

If two chromophores are to be detected at the same time - e.g. oxyhaemoglobin (\( O_2 \text{Hb} \)) and deoxyhaemoglobin (\( \text{HHb} \)), at least two
different wavelengths will be needed. This yields the following system of equations:

\[ A_{\lambda_1} = (\alpha_{\lambda_1}^{O_2Hb} \cdot c_{O_2Hb} + \alpha_{\lambda_1}^{HHb} \cdot c_{HHb}) \cdot L \cdot DPF + \text{const}_{\lambda_1} \]

\[ A_{\lambda_2} = (\alpha_{\lambda_2}^{O_2Hb} \cdot c_{O_2Hb} + \alpha_{\lambda_2}^{HHb} \cdot c_{HHb}) \cdot L \cdot DPF + \text{const}_{\lambda_2} \]

or using matrices and vectors:

\[ A = [\alpha] \cdot c \cdot L \cdot DPF + \text{const} \]

Only changes in attenuation are evaluated.

\[ \Delta A = [\alpha] \cdot \Delta c \cdot L \cdot DPF \]

Hence the change in concentration can be calculated from a change in attenuation:

\[ \Delta c = [\alpha]^{-1} \cdot \Delta A / (L \cdot DPF) \]

If more wavelengths are used than chromophores to be detected, then a least square fit can be made with the normal equation of Gauss:

\[ \Delta c = ([\alpha]^T \cdot [\alpha])^{-1} \cdot [\alpha]^T \cdot \Delta A / (L \cdot DPF) \]

The DPF decreases with increasing wavelength. This effect has been measured and is taken into account in today's algorithms [Matcher 1995].

c) The pulse oximetric approach. Pulse oximetry measures the arterial oxygen saturation (SaO₂), which is defined as:

\[ \text{SaO}_2 = \frac{c_{O_2Hb}}{c_{HHb}} = \frac{c_{O_2Hb}}{c_{O_2Hb} + c_{HHb}} \]

where O₂Hb is the oxyhaemoglobin, HHb the deoxyhaemoglobin and tHb the total haemoglobin. Using the equation 6 for the example of two wavelengths:
\[ c_{O_2 \text{Hb}} = (\alpha_{11}^{-1} \Delta A_{\lambda,1} + \alpha_{12}^{-1} \Delta A_{\lambda,2}) \times L \times DPF \]
\[ c_{Hb} = (\alpha_{21}^{-1} \Delta A_{\lambda,1} + \alpha_{22}^{-1} \Delta A_{\lambda,2}) \times L \times DPF \]

Inserting this into equation (8):

\[ \text{SaO}_2 = \frac{(\alpha_{11}^{-1} \Delta A_{\lambda,1} + \alpha_{12}^{-1} \Delta A_{\lambda,2}) \times L \times DPF}{((\alpha_{11}^{-1} \Delta A_{\lambda,1} + \alpha_{12}^{-1} \Delta A_{\lambda,2}) + (\alpha_{21}^{-1} \Delta A_{\lambda,1} + \alpha_{22}^{-1} \Delta A_{\lambda,2})) \times L \times DPF} \]

\[ \text{SaO}_2 = \frac{(\alpha_{11}^{-1} \Delta A_{\lambda,1} + \alpha_{12}^{-1} \Delta A_{\lambda,2})}{((\alpha_{11}^{-1} \Delta A_{\lambda,1} + \alpha_{12}^{-1} \Delta A_{\lambda,2}) + (\alpha_{21}^{-1} \Delta A_{\lambda,1} + \alpha_{22}^{-1} \Delta A_{\lambda,2}))} \]

Hence it is not necessary to know L or DPF to calculate \text{SaO}_2.

To measure the \text{SaO}_2 the changes in attenuation used are caused by the pulsations of the heart. With each systole a pressure wave spreads out along the arteries and for a moment there is a higher blood content in the tissue. It is assumed, that these pulsations originate purely from arterial blood.

For the detection of the \text{SvO}_2, pulsations of the veins had to be found. As described above, those pulsations were found in the pulsations originating from the ventilation pressure.

### 7.4.2. Filters

The filtering to separate the heart rate pulsation and the ventilator rate pulsation has to be adjusted to the heart rate as well as the ventilator rate, which is different from one patient to another and may even change within one individual. The main filters were therefore implemented by software. To avoid effects like phase shifts symmetrical filters had to be used. The filters implemented for our purpose, were digital band pass filters, with a depth of 1024 samples [Best 1991, 1993].

The right choice of filters is a crucial problem for the distinction of \text{SaO}_2 and \text{SvO}_2 from the same signal. The frequency of the ventilator and the heart rate differs sometimes only by a factor of two.
7.4.3. Maximum and minimum detection

There are different techniques to detect the maximum and minimum attenuation of the two pulse waves, once they have been separated. The simplest way, is taking the derivative with respect to time. This can be easily implemented by taking the difference from one sample to the next. There are two problems with real pulse wave signals:
1. There often is a physiological drift of the baseline from one pulse to the next.
2. The signals contain a certain amount of noise, which is amplified by taking the derivative.
Both problems are solved by using a good digital band pass filter with a rectangular window in the frequency domain, by which slow changes and high frequency noise can be eliminated.

7.4.4. Optimal wavelengths

Light penetrates deepest into tissue in the near infrared band between 650nm and 945nm. Below 650nm haemoglobin and above 945nm water is strongly absorbing. Thus, for an emitter detector distance of more than 2cm only the band between 650nm and 945nm is feasible. The optimal wavelengths should be chosen according to three points of view:
1. Sensitivity: A change in oxygenation should lead to a maximum change in attenuation. This means, that the extinction coefficients for oxyhaemoglobin and deoxyhaemoglobin must be as different as possible for the wavelengths used in the algorithm. As a result, the coefficients in the algorithm (equation 7) become minimal. A simple measure of the efficacy of the algorithm therefore is the sum of the absolute values of the coefficients of the algorithm.
2. Specificity: The wavelengths should be resistant to movement artefacts. During a movement there may be physiological changes in oxygenation or blood concentration. These changes are not artefacts and have to be distinguished from movements, where the sensor position or spacing is altered. During such an alteration, there is a change in attenuation, which is due to the different amount of brain between emitter and detector. For this study, we assume, that the amount of skin or skull penetrated is roughly the same, when the emitter detector spacing is changed. It is important, that the change in
attenuation due to a varying path through brain tissue is not converted into haemoglobin concentrations. The absorption spectrum of brain is approximately constant between 650nm and 945nm, which is true for bone and skin too [van der Zee 1992]. Therefore the concentration change in oxyhaemoglobin and deoxyhaemoglobin calculated by the algorithm to a step change of one optical density was used as a measure of specificity.

3. **Tissue sampling:** The scattering of tissue decreases with increasing wavelength. This means, that the depth of penetration may vary for the different wavelength. Therefore the wavelengths should be as close together as possible in order to investigate the same sample of tissue with all wavelengths. It is obvious, that the three cited criteria can not be fulfilled ideally. For the first two criteria the optimal sets of wavelengths were found numerically. A program to test all possible algorithms between 650nm and 945nm in steps of 5nm for three, four, five and six wavelengths was implemented in turbo pascal. The solutions for optimum sensitivity are shown in table 1. The most specific solutions are shown in table 2.
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Table 1: These are the five sets of optimal combinations of wavelengths with respect to sensitivity using three, four, five or six wavelengths. The smaller the number for the sensitivity or specificity the better. The most important wavelengths are 650nm and 945nm. The third important wavelength is a bit above the isobestic point at 815nm [Zijlstra 1991], where oxy- and deoxyhaemoglobin have equal extinction coefficients.
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Table 2: These are the five sets of optimal combinations of wavelengths with respect to specificity using three, four, five or six wavelengths. The smaller the number for the sensitivity or specificity the better. Contrary to the best sensitivity the optimum wavelengths are close together.

It is impossible to find a general solution. For each situation it has to be considered, which of the three criteria is the most important.

In near infrared spectrometry a correction for the differences of the amount of tissue sampled by each wavelengths is made. This correction fixes a differential pathlength factor for each wavelength. However it has been shown [Cope 1993], that this has only little influence on the calculated oxy- or deoxyhaemoglobin concentrations.
7.5. Clinical Results

7.5.1. Procedure

The photometer was tested in the clinic for neonatology. For ethical considerations only clinically stable infants, who needed additional oxygen and were mechanically ventilated, were included in this study. The study was approved by the ethical committee. The goal of the study was to measure the SvO₂ in 15 infants and to find evidence of the validity of the measurements. For this purpose each infant was given a bolus of oxygen to show a time difference in the rise between SaO₂ and SvO₂. Furthermore the cerebral blood flow was calculated and set in relation to the oxygen extraction. Another possible evidence is the expected inverse correlation of oxygen extraction and pCO₂ (see chapter 3.4).

7.5.2. Infants

From 15 infants measurements were obtained. All infants were mechanically ventilated and needed additional oxygen. The sensors were fixed at the forehead with an elastic bandage. All infants were given two consecutive boli of oxygen. The measurements did not last for more than 5min. In 5 infants the measurements had to be discarded due to the following reasons: The infants were either moving during the measurement procedure or they were breathing themselves. This is possible, because tubes for neonates are not fixed airtight and allow own breathing efforts. In the recovery phase the infant is even encouraged to breathe by itself by reducing the ventilator rate. In one infant the ventilator rate pulsation was missing for no discernible reason.

The remaining 10 infants had a gestational age of median 29 5/7 (range: 26 3/7 to 36) weeks, a birthweight of 1555 (720 to 2500) g and a postnatal age of 4 (1 to 10) days.
7.5.3. Signal analysis

The signals had to be analysed with respect to three results:
1. The pulse wave corresponding to the heart rate.
2. The pulse wave corresponding to the ventilator rate
3. The quick oxygenation increase.

Therefore the data were filtered for 1. and 2. For 3. the data were converted into oxyhaemoglobin concentrations (O$_2$Hb) and total haemoglobin concentration (tHb) by the algorithm used in near infrared spectrophotometry (see chapter 7.4: equation 7). For this purpose the pulse waves were of no interest and the data were converted to 0.5s sample time by averaging 50 samples. A differential path length factor of 3.8 was used [Benaron 1995 Duncan 1995, van der Zee 1992, Wyatt 1990].

Figure 9: The pulsations of the light attenuation. Shown in the middle is the raw signal. Using the appropriate band pass filters, the heart rate and ventilator rate pulsation can be separated from the raw data. The baselines are arbitrary.
Figure 10: A quick oxygenation increase, where the cerebral oxyhaemoglobin (O$_2$Hb) increases quickly while the total haemoglobin (tHb) remains approximately stable.

7.5.4. Quick change in oxygenation

The quick oxygenation increase caused a change in attenuation, which was a few times bigger, than the one of the two pulsations. Therefore the filters were only able in a few cases to separate the two pulsations during the quick increase. This was particularly true for the SvO$_2$. 
Figure 11: An example, where it was possible to separate the two pulse waves correctly during the quick oxygen change. At 68s the arterial oxygen saturation ($SaO_2$) starts to increase. The venous saturation has a delay of about 10s. The bolus of oxygen arrives first in the arterial system, passes the brain and then reaches the venous system.

Due to this problem it was only possible to evaluate the cerebral blood flow in 5 infants (table 3) and the delay in the venous increase compared to the arterial increase could only be seen clearly in one infant (figure 11). All other infants had either noisy increases, where the start of the increase could not be clearly identified or the increase was not visible at all.

7.5.5. Arterial and venous saturation

During the evaluation procedure the periods of time, which had reliable pulse waves (e.g. low noise, no phase shifts between wavelengths) were identified and their oxygen saturations were averaged (table 3).
Table 3: Detailed results for the 10 infants: GA = gestational age (weeks), BW = birthweight (g), PA = postnatal age (days), HR = heart rate (beats/min), pCO₂ = partial carbon dioxide pressure of the blood measured transcutaneously (kPa), VR = ventilator rate (1/min), VPH = highest ventilator pressure during inspiration (mbar), VPL = lowest ventilator pressure during expiration (mbar), FiO₂ = fraction of inspired oxygen (%), SaO₂ = arterial oxygen saturation (%), SvO₂ = venous oxygen saturation (%), OE = oxygen extraction (%) and CBF = cerebral blood flow (ml/(100g*min)).

It was found, that the mean SaO₂ was 89.9% (SD 5.4%). This is slightly lower than the pulse oximeter readings. This difference can either be explained by the different tissue, which is sampled (brain instead of the right hand) or a systematical underestimation due to the use of the near infrared spectrophotometry algorithm [Wyser 1994].

The mean SvO₂ was 73.0% (SD 8.9%). The SvO₂ was always lower than the SaO₂, although in some cases it was not significant.

The mean oxygen extraction was 16.9% (11.7%).

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Figure 12: The arterial and venous oxygen saturations (SaO₂ and SvO₂) of the 10 infants are shown.

7.5.6. Correlation with pCO₂

A significant inverse correlation between pCO₂ and the oxygen extraction was found (figure 13). From the physiologic point of view this is reasonable, because a high pCO₂ is correlated with a high cerebral blood flow, which is correlated with a low oxygen extraction.
Figure 13: There is an inverse correlation between the partial carbon dioxide pressure (pCO₂) and oxygen extraction (p<0.05). A high pCO₂ is correlated with high cerebral blood flow and inversely correlated with oxygen extraction.

7.5.7. Discussion

By tilting the infants head down [Skov 1993] the cerebral SvO₂ observed was 53.4% (SD 15.4%) in preterm and 67.3% (SD 9.4%) in asphyxiated term infants. Two of the infants in our study were preterm and asphyxiated and had a SvO₂ of 63.7% respectively 53.8%. Our findings are lower for asphyxiated infants and higher for the preterm infants.

Validation of this method to measure SvO₂ is needed. This is difficult, because jugular bulb occlusion and tilting increase intracranial pressure and are not a gold standard. Furthermore both methods, increasing the intracranial pressure, may cause cerebral haemorrhage.

As evidence of the reliability of our method, there is a significant negative correlation between transcutaneous partial carbon dioxide tension and oxygen extraction.

There was no apparent correlation between gestational age and oxygen extraction. In three infants the oxygen extraction was below 10%. In accordance with our findings Altman (1993) found two newborn infants with very low oxygen consumption by PET.
This method involves no ionising radiation, needs no calibration and is noninvasive. It could be used like pulse oximetry to monitor adults and infants continuously.
8. Improved Monitoring of Preterm Infants by Fuzzy Logic

(Technology and Health Care, in press)

8.1. Abstract

Keeping the oxygenation status of newborn infants within physiologic limits is a crucial task in intensive care. For this purpose several vital parameters are supervised routinely by monitors, such as electrocardiograph, transcutaneous partial oxygen pressure monitor and pulse oximeter. Each monitor issues an alarm signal whenever an upper or lower limit of the parameter(s) measured is exceeded. However, in practice it turns out, that a considerable amount of false alarms is generated by artefacts, which are attributed mostly to movements of the infants. Eliminating these false alarms would be of benefit to the staff as well as the patients of the intensive care unit. Accordingly, an automated system based on Fuzzy Logic system was developed, which is capable of distinguishing between critical situations and artefacts.

The system is based on a Transputer IMS T425 in a PC, which collects the data from the monitors, plots it on a colour screen, saves it to hard disk and analyses it by Fuzzy Logic. Fuzzy algorithms were developed to generate more reliable alarms.

All vital parameters of eight infants, who either moved often and/or frequently produced real alarm situations, were recorded. Synchronously the infants' movements and care procedures were video taped. The data and video were analysed off line with the help of an experienced neonatologist. His judgement was compared to the analysis of the Fuzzy Logic system.

The results show that it is possible to improve the reliability of the monitored data with the aid of an evaluation strategy based on Fuzzy Logic and hence distinguish between real alarm situations and movement artefacts to the extent that an application in an intensive care unit under routine conditions becomes conceivable.
8.2. Introduction

A major task in neonatal intensive care consists of controlling the oxygenation status of the infants and keeping the relevant parameters within physiological limits. Thereby it has to be noted that an excessive as well as an insufficient oxygenation can be harmful, in particular to the brain. Therefore, several parameters are monitored routinely: the electrocardiograph (Hellige, Freiburg, Germany) measures the heart rate (HR in beats/min), the oxymonitor (Hellige) the transcutaneous partial oxygen pressure of the blood (pO₂ in kPa) and the pulse oximeter (Nellcor, Hayward, USA) the arterial oxygen saturation (SaO₂ in %) and pulse rate (PR in beats/min) (figure 1).

Figure 1: A newborn infant in the incubator. To keep the oxygenation status within physiologic limits sensors are attached to the right foot (pulse oximeter), the stomach (transcutaneous partial oxygen pressure monitor) and the sides of the chest (electrocardiograph).
All of these monitors use upper and lower limits which reflect the normal physiological range of the quantity under consideration. Whenever a limit is exceeded an alarm is produced. However, false readings may occur, which are mostly due to artefacts caused by movements of the infant. Accordingly, a considerable amount of false alarms is generated [Lawless 1994]. It would be of benefit for the staff as well as the patients of the intensive care unit, if these false alarms were eliminated. For this purpose an automated monitoring system was developed, which uses Fuzzy Logic to distinguish between artefacts and critical situations, such as hypoxias (insufficient oxygenation of the blood) and moderate or severe apneas (cessation of spontaneous breathing for 15 to 30s or for more than 30s, respectively).

Apart from artefacts, another, more fundamental problem arises. According to present practice, the trigger alarms of the different monitors are set at fixed levels, e.g. the pulse oximeter alarm is set at a lower limit of 85%. This means, that an \( \text{SaO}_2 \) of 85.1% is considered sufficient, while one of 84.9% is not. Yet, in such cases the conventional logic with the two fixed steps ("true" and "false") is not appropriate, because such fixed steps do not correspond to the real physiological situation. If all other parameters are within a normal range, an infant will be fine with a saturation of 84.9, while 85.1 may be too low, if other parameters are affected as well.

The main advantage of Fuzzy Logic [Zimmermann 1991, Tilli 1993] is twofold. First, a strategy can be devised which allows to eliminate artefacts and to distinguish them from critical situations. Second, a system based on Fuzzy Logic has the ability to systematically process uncertainty or vague data. In terms of Fuzzy Logic, it could be defined that 85% has a membership of 0.5 of the Fuzzy set "too low" and a membership of 0.5 of the Fuzzy set "normal", which means that there is a probability of 50% that the value is too low and a probability of 50% that the value is normal (figure 2). The system presented in the following is designed to take full advantage of the possibilities offered by Fuzzy Logic. The system is implemented in C using the software development tool Fuzzyshell of Tilli (Aachen, Germany).
Figure 2: The two Fuzzy sets "too low" and "normal". Each saturation value has a certain membership to one or both of the Fuzzy sets. E.g.: A saturation of 85% has a membership of 0.5 of "too low" and 0.5 of "normal".

8.3. Experimental Procedures

8.3.1. Implementation

In our concept we decided to use transputers as core element, because of the various advantages they offer. First, transputers have a built in communication facility, which allows to build an efficient and simple networking [INMOS 1990, Hinton 1993]. Second, the technical implementation can be tested with one transputer alone, which processes the data of one patient. The hardware is plugged into a PC, which can easily be adapted later on to control the data of all the patients of the intensive care unit by plugging in more transputer-modules.

The data logging systems, which are commercially available today, require one PC per patient. This is expensive and requires a lot of space, which is scarce in most intensive care units.
Figure 3: The incoming analogue data from the monitors are low pass filtered, converted into a digital signal, buffered in a FIFO and then processed by the transputer. The PC saves and displays the data. For each patient such a module is used and inserted in the same PC. The entire intensive care unit can therefore be served by a single PC, saving cost and space.

In our one-patient module, we restricted ourselves to eight channels, which can be collected simultaneously, as this is sufficient to monitor one patient completely. The data from the monitors described above is available in analogue format. Prior to A/D conversion, a programmable low pass filter prevents aliasing. The signals then pass a 12 bit AD converter, are buffered in a FIFO and transferred to the transputer. The system uses a transputer IMS T425 with 1MByte of RAM (figure 3). The transputer was programmed in Parallel C from 3L Ltd (Edinburgh, UK), which supports parallel processing.
8.3.2. Algorithm

There are four conditions, which the Fuzzy system is able to detect.

1. **Movement artefacts.** An infant which is moving or crying may cause the monitors to give imprecise or even totally faulty measurements (figure 4). Especially the pulse oximeter is sensitive to movements.

2. **Moderate apneas.** A moderate apnea is defined as a cessation of breathing for a duration of 10s to 30s (figure 5). During such an event, the values of SaO₂ and transcutaneous pO₂ usually remain in a normal range, but the heart rate may be slightly depressed. The infant can either recover on its own or go on into a severe apnea.

3. **Severe apneas.** A severe apnea is a cessation of breathing for more than 30s (figure 5). In such situations, it is not clear whether the infant resumes breathing on its own. During that time the oxygenation of the blood of the infant drops below the alarm limits.

4. **Hypoxia.** The infant is breathing too superficial and pO₂ as well as the saturation drop for more than 30s. In such situations the oxygenation may become definitely insufficient and the intervention of a nurse to stimulate breathing is required (figure 6).
Figure 4: The upper plot shows the heart rate from the electrocardiograph and the pulse rate from the pulse oximeter. An alarm is triggered, if either one is lower than 90 beats/min or higher than 240 beats/min. In the lower plot the arterial oxygen saturation (alarm limits: 85% and 95%) from the pulse oximeter and the partial oxygen pressure (alarm limits: 6kPa and 13kPa) from the partial oxygen pressure monitor are shown. At 1.5 min a movement of the infant causes a wrong measurement of the pulse oximeter: Thus arterial oxygen saturation as well as the pulse rate drop to 0 for 10s, which is physiologically impossible. More difficult to detect are artefacts such as between 5 min and 10 min, where the pulse rate and saturation give incorrect values without dropping to zero. Such artefacts will trigger a false alarm. Pulse rate and heart rate should always have the
same values. A difference between these two signals usually indicates an unreliable measurement of saturation and pulse rate.

Figure 5: The plots are in analogy with the ones in figure 4. At 30s and at 3min two severe apneas and at 5min one and at 7min three consecutive moderate apneas of 14s to 20s duration occur, all accompanied by a drop in heart rate, partial oxygen pressure and saturation. During the moderate apneas the infant stops breathing and starts again on its own. Severe apneas usually require the intervention of a nurse. The three consecutive
Figure 6: The plots are in analogy with the ones in figure 4, now showing a typical hypoxia. The oxygenation slowly decreases over a period of 2min, because the infant is breathing superficially. At 3.5min the infant is definitely underoxygenated. Such situations require the intervention of a nurse, who either stimulates the infant or supplies more oxygen.
From various algorithms tested the best results were obtained using the following strategy: From the four signals (HR, pO₂, SaO₂, PR) three (HR, pO₂, SaO₂) are directly fed into the algorithm. Two additional inputs are generated as the difference between HR and PR on the one hand and the derivative with respect to time of the pO₂ curve (increasing or decreasing tendency) on the other hand. For all five inputs three to five membership functions (e.g.: low, normal, high) are defined as explained in figure 2. 16 rules are defined, which link various combinations of inputs and their memberships to a "likely" or "unlikely" alarm.

<table>
<thead>
<tr>
<th>rule</th>
<th>HR-PR</th>
<th>SaO₂</th>
<th>pO₂</th>
<th>HR</th>
<th>ΔpO₂</th>
<th>alarm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>small</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td></td>
<td>unlikely</td>
</tr>
<tr>
<td>2</td>
<td>small</td>
<td>normal</td>
<td>low</td>
<td>low</td>
<td></td>
<td>likely</td>
</tr>
<tr>
<td>3</td>
<td>small</td>
<td>low</td>
<td>normal</td>
<td>low</td>
<td></td>
<td>likely</td>
</tr>
<tr>
<td>4</td>
<td>small</td>
<td>low</td>
<td>low</td>
<td></td>
<td></td>
<td>likely</td>
</tr>
<tr>
<td>5</td>
<td>small</td>
<td>low</td>
<td>low</td>
<td></td>
<td></td>
<td>likely</td>
</tr>
<tr>
<td>6</td>
<td>small</td>
<td>low</td>
<td>low</td>
<td></td>
<td>decreasing</td>
<td>likely</td>
</tr>
<tr>
<td>7</td>
<td>small</td>
<td>low</td>
<td>low</td>
<td></td>
<td>decreasing</td>
<td>likely</td>
</tr>
<tr>
<td>8</td>
<td>small</td>
<td>low</td>
<td>low</td>
<td></td>
<td>low</td>
<td>likely</td>
</tr>
<tr>
<td>9</td>
<td>low</td>
<td>normal</td>
<td>normal</td>
<td>low</td>
<td>decreasing</td>
<td>likely</td>
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<tr>
<td>10</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td>unlikely</td>
</tr>
<tr>
<td>11</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
<td>unlikely</td>
</tr>
<tr>
<td>12</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>slightly increasing</td>
<td>increasing</td>
<td>unlikely</td>
</tr>
<tr>
<td>13</td>
<td>slightly low</td>
<td>normal</td>
<td>normal</td>
<td>slightly increasing</td>
<td>increasing</td>
<td>unlikely</td>
</tr>
<tr>
<td>14</td>
<td>slightly low</td>
<td>normal</td>
<td>normal</td>
<td>increasing</td>
<td>unlikely</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>highly-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unlikely</td>
</tr>
<tr>
<td>16</td>
<td>highly-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unlikely</td>
</tr>
</tbody>
</table>

The main set of rules classifies situations as normal or abnormal, in particular: if the pO₂ is low and the SaO₂ is low and the difference between HR and PR is small, then an alarm will be likely (rule 4). If the pO₂ and the SaO₂ are normal, then an alarm will be unlikely (rule 1). A smaller set of rules qualifies the reliability of the signals using the redundancy of the signals HR and PR (rules 15 and 16). The membership of the "if" part of each rule is aggregated using the minimum operator [2,3], which corresponds to the "and" operator in
conventional logic. The algebraic product operator \([2,3]\) as inference determines to which degree the "then" part is true for each rule considering the result of the aggregation. The "then" parts from all the rules are then combined using the maximum operator \([2,3]\), which corresponds to the "or" operator in conventional logic. The result corresponds to a two-dimensional geometric area. To get a value as output, the centre of gravity is used as defuzzificator.

8.3.3. Testing Procedure

Eight infants, which were known to either move often and/or produce apneas, were included in this study. The infants had a gestational age of median 28 1/7 weeks (range from 25 4/7 weeks to 31 4/7 weeks), an age of 20 days (2 days to 57 days) and a birthweight of 1020g (900g to 1417g). HR, PO\(_2\), SaO\(_2\), PR and breathing movements (in 1 case only) were recorded. At the same time, a synchronised video filmed the infants' movements and the care procedures of the nurses. The data and video were analysed off line with the help of an experienced neonatologist. The events were classified according to the four definitions mentioned above. This classification was assumed to be the gold standard to which the analysis of Fuzzy Logic was compared.

8.4. Results

Data from a total of eighteen hours were recorded. During that time 384 alarms occurred. The retrograde analysis revealed that of these alarms 48 were correct and 336 were false. The correct alarms included 16 moderate apneas, 8 severe apneas and 24 hypoxias. The performance of the Fuzzy system is as follows:
<table>
<thead>
<tr>
<th>classification</th>
<th>correct</th>
<th>false</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate apneas</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>severe apneas</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>hypoxias</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>movement artefacts</td>
<td>334</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 7: The Fuzzy Logic system returns this Fuzzy variable, when the data from figure 4 is processed. A value around 300 indicates a normal physiologic condition. The higher the values are, the more critical the situation is for the infant. For our study it was assumed, that an alarm will be triggered, if the values are above 500. It shows, that during all movement artefacts the Fuzzy variable remains clearly below this level and no false alarm occurs.
Figure 8: In analogy with figure 7 the Fuzzy variable, which results when the data from figure 5 are processed by the Fuzzy system, is shown. The analysis reveals all apneas as clear increases in the Fuzzy variable.

Figure 9: In analogy with figure 7 the Fuzzy variable, which results when the data from figure 6 are processed by the Fuzzy system, is shown. The hypoxia is reliably detected by the Fuzzy system.
Accordingly, the Fuzzy system would have avoided 99.4% of all false alarms, but it would have missed two moderate apneas. It is expected, that these apneas would be correctly detected, if they had developed into a severe apnea.

8.5. Discussion

By excluding false alarms, the developed Fuzzy Logic system will considerably reduce stress for the nurses. They will be able to focus on the infants needing care, because they will be less distracted by false alarms. The new alarms are more reliable and will be taken more seriously.

The system is not only reliable, it is simple, inexpensive and flexible as well. Although it was developed for newborn infants, it could easily be adapted for adult intensive care.

In physiology there are a lot of vague limits and measurements of uncertain quality. Fuzzy Logic would be suitable for such purposes as well.

8.6. Conclusion

In conclusion, this first application showed a favourable performance of the system. Ultimate acceptance will have to be established in a more extended study involving more patients and a longer duration.
9. Conclusion

The most important factors to judge the oxygenation status of the neonatal brain are the cerebral haemoglobin concentration, cerebral blood flow, cerebral arterial and venous oxygen saturation, the oxygen offer, oxygen consumption and oxygen extraction.

The methodology to evaluate slow changes of oxygenation to measure cerebral haemoglobin concentration, was developed for this thesis (chapter 4). In particular a set of quantitative criteria, which describes the quality of a single measurement was established. The method is currently applied in the Clinic for Neonatology in Zurich to find normal values of cerebral haemoglobin concentration for preterm infants.

The methodology how to analyse quick changes in oxygenation to measure cerebral blood flow is described in chapter 5. This method is now used in the Clinic for Neonatology in Zurich as well as in many centres in Europe, where the method was established under the conduction of the author in the frame of the EU concerted action on near infrared spectroscopy and imaging.

A mathematical one compartment model was used (chapter 6) to determine the transit time of blood through the brain in addition to the above parameters. It showed, that the transit time in preterm infants was longer than in older infants.

To determine the cerebral arterial and venous oxygen saturation, a photometer with high time resolution was developed (chapter 7). Both parameters can be measured continuously. For the first time a non-invasive technique provides continuous data not only on the oxygen offer, but also on the oxygen extraction. The method will be used to establish normal values for venous oxygen saturation.

Applying a combination of the above techniques the remaining parameters (oxygen offer and oxygen consumption) can be determined.

The optical techniques described are non-invasive and can be performed at the bedside. They give important information to determine how much oxygen should be given to preterm infants.

Fuzzy Logic was applied to determine the condition of preterm infants using the continuous data, which is available routinely in the intensive care unit (chapter 8). The system was able to eliminate movement artefacts and detect critical situations reliably. It was shown, that Fuzzy
Logic is appropriate to monitor the oxygenation status of a patient in a clinical environment.

9.1. Future perspective

The measurement of cerebral haemoglobin concentration and cerebral blood flow is only intermittent and limited to infants, who need a higher oxygen concentration than is provided in air. In the near future this will probably be improved for the cerebral haemoglobin concentration. The solution of this problem mainly depends on the development of a valid model for light transport through the head. To measure cerebral blood flow continuously will be much more difficult, because there is presently no alternative to the current intermittent principle, which is based on a dynamic concentration change of a tracer.

For the two parameters mentioned as well as for the cerebral arterial and venous oxygen saturation the normal values have to be established and the clinical relevance has to be tested.

The investigation of tissue by light is impeded by two major problems: the limited distance of penetration: the light is attenuated approximately by a factor of 10 per cm of tissue on the one hand and the difficulty of quantifying concentrations in multiply scattering multilayered tissue on the other hand. The latter can be improved by better modelling and will lead to more accurate measurements. The aim of the research in this field is a continuous non-invasive method of in vivo biochemical diagnosis and the potential to develop an imaging of parts of the body like the neonatal head and the female breast.

Fuzzy Logic has a great potential in medical diagnostic. The study shown in this thesis is only one example of many possible applications. A poster at the meeting of the "Schweizerische Gesellschaft für Intensivmedizin" was received with great interest and won the first price. The main advantage is, that using Fuzzy Logic, comprehensible and effective models can be created in a short time.
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**Curriculum vitae**

On April 11th 1965 I was born in Zurich, Switzerland. Being in the USA for one year, I received the American High School Diploma in 1983 from the John Jay High School, Katonah-Lewisboro, New York. Back in Zurich I graduated in 1984 with the Matura Typus D from the Kantonsschule Freudenberg in Zurich Switzerland. I began studies at the Swiss Federal Institute of Technology in Zurich (ETHZ), where I received the degree of electrical engineer in 1990. Since that time I am working as a research assistant in the Department of Biomedical Engineering (ETHZ and University Zurich) and in the Clinic for Neonatology, University Zurich.
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