

**NON-INVASIVE
INTRACRANIAL PRESSURE MONITORING
IN INFANTILE HYDROCEPHALUS**

**and
the relationship with transcranial Doppler,
myelination and outcome**

P.W. Hanlo

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myelination and outcome

**NIET-INVASIEVE INTRACRANIELE DRUKMETING
BIJ JONGE KINDEREN MET HYDROCEPHALUS**
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus Prof. Dr J.A. van Ginkel,
volgens het besluit van het college van Decanen
in het openbaar te verdedigen
op dinsdag 17 oktober 1995
des namiddags te 4.15 uur

door

Patrick Winfried Hanlo
geboren 25 juli 1958 te Eindhoven

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Prof.Dr C.A.F. Tulleken

Co-promotor: Dr R.H.J.M. Gooskens

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'What's past is prologue'

William Shakespeare, *The Tempest* (1611)

What's past is prologue
What's done is done
What's to come is yet to come
What's to be is yet to be

What's past is prologue
What's done is done
What's to come is yet to come
What's to be is yet to be

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aan mijn ouders

aan Els

aan mijn ouders

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Hanlo PW, Gooskens RHJM, Nijhuis IJM, Faber JAJ, Peters RJA, Van Huffelen AC, Tulleken CAF, Willemse J. The value of transcranial Doppler indices in predicting raised intracranial pressure in children with hydrocephalus. *Child's Nervous System* 1995; *in press (Chapter 4)*.

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List of abbreviations

AFP	anterior fontanelle pressure
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
CVR	cerebrovascular resistance
EDFV	end-diastolic flow velocity
ICP	intracranial pressure
IVP	intraventricular pressure
MABP	mean arterial blood pressure
MCBF	mean cerebral blood flow
MFV	mean flow velocity
NDT	neurodevelopmental testing
PD-curve	pressure depth curve (RTT)
PI	Pulsatility Index
RI	Resistance Index
RTT	Rotterdam Teletransducer
SPFV	systolic peak flow velocity
TCD	transcranial Doppler
TST	Trans Systolic Time
VPS	ventriculoperitoneal shunt
VSR	ventricle-skull ratio

CHAPTER 1

GENERAL INTRODUCTION

The incidence of hydrocephalus is approximately 1 - 3 in 1000 live births. Although great efforts have been made toward the understanding and management of hydrocephalus, the problem has not been completely solved. The specific details and dynamics of cerebrospinal fluid (CSF) absorption, the mechanism of ventricular dilatation and the physical qualities of the cerebral parenchyma, still need to be fully worked out (Aronyk, 1993).

In this introduction some historical considerations regarding diagnosis and treatment in hydrocephalus are briefly summarized, followed by a justification of the present study on monitoring intracranial dynamics in infantile hydrocephalus. The chapter ends with an outline of the aims of the study.

Historical considerations

Vesalius described a child with hydrocephalus in about 1550 and was the first to recognize the accumulation of CSF within the ventricular system (Russell, 1949). Morgagni (1682-1771) provided the initial detailed description of the pathology of hydrocephalus. He described the enlargement of the skull, associated with widening of the cranial sutures and bulging of the fontanelle, in young children with hydrocephalus (Torack, 1982). Von Haller (1708-1777) provided the physiological framework for hydrocephalus, with his extensive animal experiments (Torack, 1981). Whytt (1714-1766) later described the consequences of raised intracranial pressure (ICP) in hydrocephalus (Whytt, 1768).

Morgagni reported the existence of two types of hydrocephalus: aqueductal stenosis (obstructive hydrocephalus) and communicating hydrocephalus. Whytt was the first to distinguish between internal and external hydrocephalus. To date, researchers are still discussing the theories concerning the definition and classification of hydrocephalus (Mori, 1990; Raimondi, 1994).

Hydrocephalus has long been known as a potentially fatal disease with inevitable progression, and before surgical intervention became possible, there was little that could be done to halt the problem. Through the ages many different drugs (thyroid extract, acetazolamide, isosorbide, digoxin), and several non-surgical procedures, such as heliotherapy (compressive head-wrapping), have been tried, but all have failed (Di Rocco, 1991). Up to the present time, surgical intervention has offered the only hope for the control of hydrocephalus.

It was Walter Dandy (1886-1946) who changed the course of hydrocephalus management. In his experiments he established the true dynamic pathology of hydrocephalus and described the possible surgical principles of management (Dandy and Blackfan, 1914). In 1918 Dandy developed air ventriculography as a means of demonstrating images of the brain and its fluid spaces during life (Dandy, 1918a). Using a dye study to determine the nature of the hydrocephalus syndrome, he classified hydrocephalus as either communicating or non-communicating (obstructive), terms which are still used in clinical practice today. In cases of non-communicating hydrocephalus, due to aqueductal stenosis, Dandy advised a direct surgical approach, whereas in cases of communicating hydrocephalus he advocated choroid

plexectomy (Dandy 1918b, 1920). Operative mortality however, was high and neither of the interventions seemed able to control the hydrocephalic process.

In the late 19th century the continuous external drainage procedure was also established, but in clinical practice it proved not to be a long-term solution. Quincke (1891) described intermittent lumbar taps to control hydrocephalus, and this was followed in the first half of the 20th century by the development of several procedures for continuous drainage of the CSF from the ventricles to the subcutaneous spaces, subdural spaces, subarachnoid spaces or into the venous system, peritoneal or pleural cavity and even into the urinary tract system or gall bladder. Many attempts were also made to perform spinal drainage of CSF into the retroperitoneal space, the peritoneal cavity and the omentum or serosa of the bowel. Torkildsen (1939) devised a shunt from the lateral ventricle to the cisterna magna with, unfortunately, a rather high complication rate. It was not until 1946 that Matson (Matson, 1949) developed the first shunt valve. CSF diversion, using materials other than silicon compounds however, was doomed to failure. The overall mortality rate was about 50%, whilst 30% of the survivors suffered from moderate to severe disability (Hirsch, 1992).

In the second half of the 20th century a turning point in the treatment of hydrocephalus was realized with the introduction of the Holter silicon shunt valve (1956), and treatment of hydrocephalus became really efficient. The overall mortality rate decreased to approximately 15%, with survival rates and long-term outcome improving ever since. We now know that a series of hydrocephalic syndromes exists, each of which may be characterized by a specific pathogenesis, clinical presentation, and treatment response. Therefore it can be rather misleading at the present time to discuss just long-term outcome in hydrocephalus in general. Much progress has been made in developing better CSF shunt devices for treating hydrocephalus, although there is still a great deal of research necessary before the artificial systems are ideal. Since the complications arising from vascular (ventriculo-atrial) shunts became widely known, the general consensus has been that the peritoneum is probably the best resorptive site for CSF (Ames, 1967). Some of the complications encountered in the treatment of hydrocephalus, are due to limitations of the currently available shunt systems. In this respect, known alternative CSF diversion procedures, such as third ventriculostomy, have recently been revived for specific cases of hydrocephalus (Drake, 1993).

Justification of the study

Besides the strategy choice for CSF diversion and the treatment decision, as to whether or not to operate, the actual timing of a possible surgical intervention is sometimes very difficult to determine. Whether or not compensation of the hydrocephalic process occurs, and at what cost to the patient, is obviously a highly complex question in clinical practice (McLone and Partington, 1993). Although shunt implantation may not be complex surgery in itself, specific expertise is necessary, to determine the right indication and the appropriate type of surgery, as well as minimizing the risk of complications. The rate of shunt infection, one of the major complications, for instance, ranges from approximately 2.6% to 38% (Marlin and Gashill, 1994). Improving diagnostic facilities in order to avoid unnecessary shunt implantation is,

therefore, essential. In this respect, the present study seeks to establish the value of ICP monitoring in infantile hydrocephalus, by investigating the relationship between raised ICP and clinical signs, and the effect of raised ICP on cerebral haemodynamics, brain maturation (myelination) and neurodevelopmental outcome.

One of the crucial issues regarding CSF drainage in hydrocephalus, is to decrease ICP and restore the intracranial dynamic balance. Clinical signs and symptoms are often unreliable in detecting progressive hydrocephalus, or in predicting raised ICP, and the benefits of ICP monitoring have therefore, been suggested in previous studies.

Following Quincke's introduction of the lumbar puncture in 1891, invasive CSF pressure measurement became possible, and more than half a century later Guillaume and Janny (1951) introduced continuous invasive ICP recording in clinical practice. Lundberg (1960) provided valuable knowledge on variations in ICP characteristics in normal and pathological conditions. Since then, interest in the pathophysiology of ICP and its clinical relevance has increased considerably. Pressure-volume studies (Gooskens *et al.*, 1985a/b) and (computerized) ICP waveform analysis have provided further insights into deteriorating intracranial dynamics. Despite the controversies surrounding its benefits and risks, continuous ICP monitoring has established its rightful place in the neurosurgical and neurological intensive care in many countries. ICP monitoring is the only way of confirming, or excluding, intracranial hypertension, providing the measurements are accurate and reliable. Although there is no definite evidence that ICP monitoring will improve outcome, it can certainly be helpful in clinical management (Miller, 1985). Interpretation of the ICP signals however, requires skill and experience. ICP measurements are most frequently used in head injury management, in both children and adults, for the purpose of monitoring the cerebral perfusion pressure (CPP: difference between the arterial blood pressure and ICP). In younger children, ICP monitoring can also be valuable in other conditions, including hydrocephalus, in which the clinical treatment decision can be very difficult to make. Invasive measuring techniques are not routinely used in these children, because of the infection risk and technical problems, especially when continuous monitoring has to be applied. Several non-invasive methods have, therefore, been developed for ICP monitoring in infants with an open fontanelle (Overweg-Plandsoen, 1991). The wide range of reference values for normal ICP in neonates and infants, mostly acquired from non-invasive measurements, is probably due to the technical and operational differences inherent to the numerous techniques used. An anterior fontanelle pressure (AFP) measurement method should meet the following demands if it is to be considered reliable: (1) the application force of the device should not interfere with the measured pressure; (2) it should be possible to calibrate the measurement equipment accurately; (3) there should be little or no drift throughout the measurement; (4) a high correlation between AFP and ventricular fluid pressure (VFP; 'golden standard') has to be established. The applanation principle (Wealthall and Smallwood, 1974) appears to be, by far, the best for fontanelle pressure measurements.

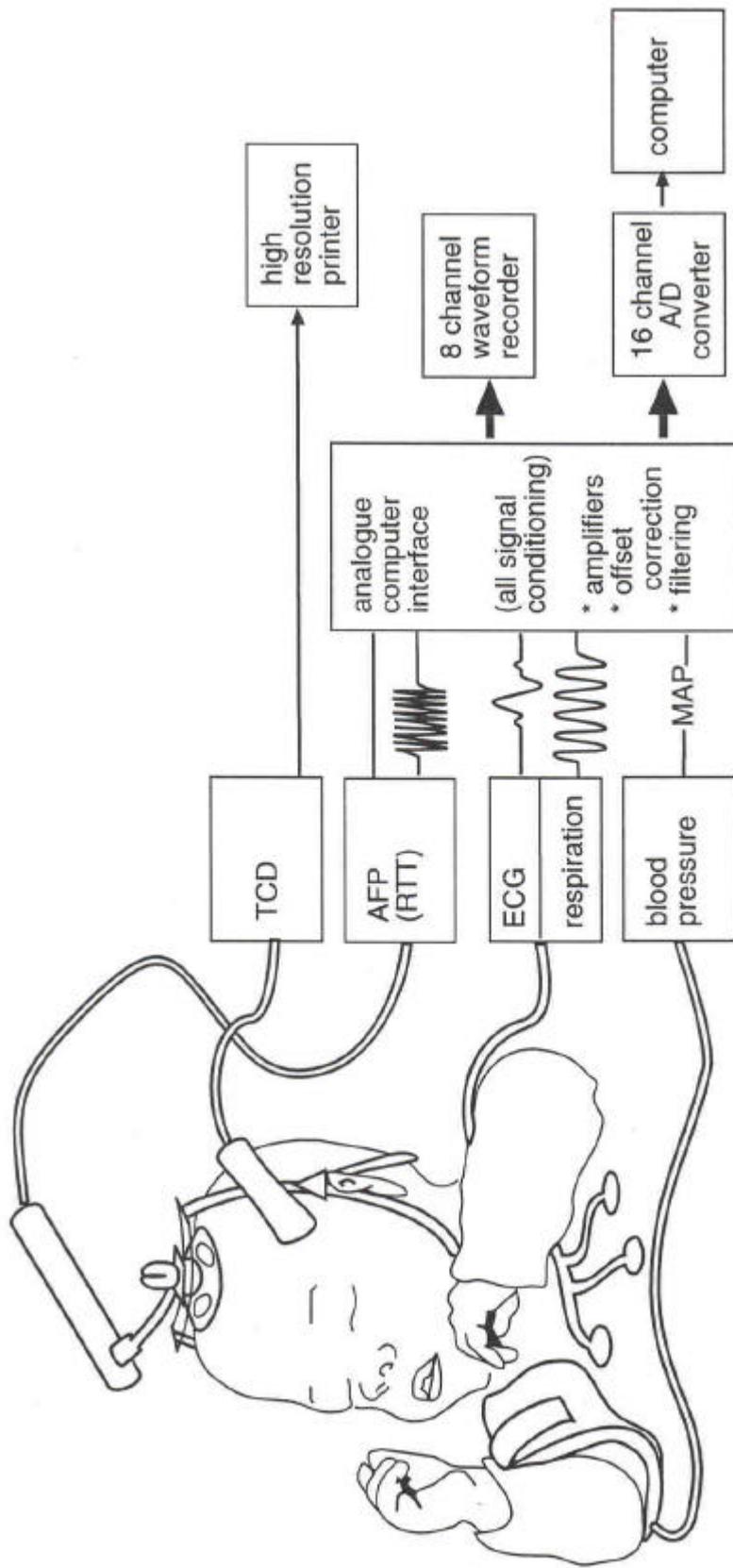
In the investigations described in this thesis, the qualities of the Rotterdam Teletransducer (RTT) are evaluated. The relationship between AFP measurements and clinical signs,

treatment decision and neurodevelopmental outcome, are investigated in infants with hydrocephalus. It has already been demonstrated that neurodevelopment in infantile hydrocephalus strongly correlates with the degree of myelination of the brain, on MR imaging, (Van der Knaap *et al.*, 1991). One of the factors influencing the process of myelination is thought to be raised ICP, although this has never been proven. In this respect, it has been stressed that the parenchymal damage results from the length of time that an increase in ICP has lasted, rather than the level the ICP has reached (Raimondi, 1994). This confirms the need for long-term measurements, since ICP shows episodic variations. Furthermore, a sequence of events leading to brain damage is postulated in the hydrocephalic syndrome: i.e. ventricular enlargement, followed by cerebral edema, obliteration of the subarachnoid spaces and aqueductal occlusion. This cerebral edema initially involves the white matter, and could indeed be another factor of delayed myelination in infantile hydrocephalus.

Raised ICP also has an effect on cerebral haemodynamics, inducing the risk of secondary ischaemic insult to the brain (Minns *et al.*, 1991; Wakayama *et al.*, 1994). The increased pressure both compresses and stretches the cerebral vasculature, thereby displacing and deforming the vessels, and causing a decrease in their calibre, which in turn results in changes in cerebrovascular resistance and cerebral blood flow (CBF). In this respect, blood flow velocity measurements in childhood hydrocephalus, using the transcranial Doppler (TCD) technique (Aaslid, 1982; Bode and Eden, 1989), have opened-up a new field of research in monitoring intracranial dynamics.

Non-invasive pressure measurements are no longer possible when the anterior fontanelle is closed. By establishing the relationship between the fontanelle pressure and the current Doppler indices, TCD could prove to be a valuable diagnostic tool for the assessment of progressive infantile hydrocephalus. The present study evaluates this relationship as also the importance of TCD waveform analysis in this context (*Scheme page 10*).

Up to the present time, no consensus on the treatment of childhood hydrocephalus has been reached (Choux, 1994). Certainly in progressive hydrocephalus, CSF diversion is the treatment of choice, for decreasing raised ICP and restoring the intracranial dynamic balance. Defining the right indication and moment at which it should be carried out, remains however, a difficult task. Therefore, critical use of ICP measurements, although little is known about their effects on outcome in children (Levene *et al.*, 1987; Doyle and Mark, 1992; Mendelow *et al.*, 1994), in combination with cerebral haemodynamic monitoring, could be helpful in the management of infantile hydrocephalus.



Scheme for computerized non-invasive ICP monitoring and interpretation

AIMS OF THE STUDY

Defining the right indication and moment of CSF diversion or shunt revision in infantile hydrocephalus is sometimes a difficult task. In order to provide an improved diagnostic approach, this study was conducted.

Aims of the study:

- To reassess the physical qualities of the Rotterdam Teletransducer (RTT) and to validate the RTT, in order to obtain reliable anterior fontanelle pressure measurements in clinical practice (*Chapter 2*).
- To establish (1) the relationship between the treatment decision as to whether or not to operate and clinical signs or anterior fontanelle pressure; (2) the relationship between clinical signs and the anterior fontanelle pressure / pressure waveform characteristics in long-term measurements in hydrocephalic infants (*Chapter 3*).
- To determine the relationship between Doppler indices and the anterior fontanelle pressure, and to evaluate the reliability of these indices, in predicting raised intracranial pressure in infantile hydrocephalus (*Chapter 4 and Chapter 5*).
- To determine the effect of raised intracranial pressure on the progress of myelination and neurodevelopment in infantile hydrocephalus (*Chapter 6*).
- To determine the value of anterior fontanelle pressure measurements in infantile hydrocephalus by studying the relationship between raised anterior fontanelle pressure, treatment strategy and outcome (*Chapter 7*).

CHAPTER 2

NON-INVASIVE INTRACRANIAL PRESSURE MONITORING IN INFANTS THE ROTTERDAM TELETRANSDUCER REVISITED

Abstract

Measurement of intracranial pressure (ICP) is important in patients at risk for raised ICP, as in hydrocephalus. Ideally, it should be non-invasive, thus avoiding the risk of infection and other complications. Such is provided by measurement of ICP through the anterior fontanelle. There are several methods for measuring the anterior fontanelle pressure (AFP); those most frequently used are based on the appplanation principle. An evaluation of AFP measurement devices resulted in the choice of the Rotterdam Teletransducer (RTT) to be used in our study of children with hydrocephalus.

The literature contains little information on the accuracy or validation of the AFP measurements using the RTT. The physical qualities of the RTT were therefore reassessed, using a specially developed calibration device. The results of this study demonstrate that the membrane temperature does not have any effect on the measured pressure. The thermal stabilization time of the RTT was found to be 3 hours after switching on. Insufficient thermal stabilization results in a pressure underestimation of up to 3 mmHg. Furthermore, a maximum inaccuracy of 2.6 mmHg, after calibration and readjustment of the transducer, was calculated.

Validation of the equipment was achieved by simultaneous AFP/ICP measurements in hydrocephalic patients showing high correlations (r : 0.96 - 0.98). The discussion suggests a measurement protocol as a means of increasing the reliability of RTT measurements.

Introduction

Intracranial pressure (ICP) monitoring in young infants can be useful in a variety of neurological conditions (hydrocephalus, intraventricular haemorrhage, birth injuries, meningitis, encephalopathies, etc.). Ideally, the monitoring should be non-invasive, avoiding the risk of infections and other complications. Because the anterior fontanelle in infants gives access to the intracranial compartment, several fontanometers for measuring ICP have been designed (Wealthall and Smallwood, 1974; Leggate and Minns, 1991). These non-invasive techniques can be applied over a longer period of time and allow frequent intermittent measurements. However, ICP monitoring is only of clinical importance when the measurement equipment is accurate and completely reliable. Measurement should show high correlation with the actual ICP. Although several studies suggest a close relation with simultaneously measured intraventricular pressure, a serious criticism of fontanometers has been that non-invasive ICP measurements are not sufficiently reliable to be useful in clinical practice (Wealthall and Smallwood, 1974; De Jong *et al.*, 1982; Plandsoen *et al.*, 1986; Mehta *et al.*, 1988; Leggate and Minns, 1991). The inaccuracy is partly caused by externally exerted pressure when applying the transducer to the fontanelle (Horbar *et al.*, 1980; Lacey *et al.*, 1986). Attention has also been drawn to problems with calibration and zero drifts (Leggate and Minns, 1991).

Most anterior fontanelle pressure (AFP) measurement techniques are based on the appplanation principle, described by Wealthall and Smallwood (1974). This involves the application of a transducer with a sensing surface, surrounded by a non-sensitive outer ring. These are positioned so that they are coplanar with the fontanelle. In this way, the skin is flattened and stretching forces are dissipated at the peripheral non-sensitive outer ring. The non-invasive AFP measurements are performed in either a direct or an indirect manner. The indirect (or pneumatic) AFP measurement technique uses air as a medium for transmitting the AFP to the pressure measurement device. With the direct AFP measurement technique, the pressure is measured directly on the fontanelle.

Indirect (pneumatic) AFP measurement devices

The pressure applied to the coplanar membrane is actively kept in equilibrium with the AFP using an external air-pump. There are two principles commonly used to detect the equilibrium between externally generated pressure and AFP.

The first principle uses optically controlled pressure regulation, in which a beam of light is reflected on a mirror, mounted on the coplanar membrane. The intensity of the reflected light is influenced by the deformation of the membrane, due to the difference between AFP and externally generated pressure. Of the optic controlled devices, the LADD, first introduced by Vidyasagar and Raju (1977), is the one most commonly used.

The second principle uses a valve to control the externally generated pressure, first developed by Whitelaw and Wright (1982). A continuous, but slow air flow is supplied to the device,

which results in pressure on the coplanar membrane. The valve opens and keeps the external generated pressure equal to the AFP.

Inherent to both techniques are certain drawbacks, such as a slow frequency response, temperature instability and motion artefacts due to movements of the connecting air tube (both devices) and optic fibres (optically controlled devices) (Bunegin *et al.*, 1987; Leggate and Minns, 1991). Furthermore, one has no means of making baseline corrections to the LADD, and in situ calibration of this device on the fontanelle is problematic (Bunegin *et al.*, 1987; Leggate and Minns, 1991).

Direct AFP measurement devices

The pressure sensor is mounted on the membrane and converts the AFP into an electrical impedance. The coupling between the sensor and the impedance measuring device can be either galvanic or telemetric. An example of a galvanic coupled device is the strain gauge transducer with the gauges placed in a Wheatstone bridge (Schettini *et al.*, 1971; Honda, 1984; Hayashi *et al.*, 1987). An example of a telemetric device is the Rotterdam Teletransducer (RTT), a telemetric high frequency tuning device based on modulation of the resonance frequency of a passive coil capacitor circuit (De Jong *et al.*, 1984a; Overweg-Plandsoen, 1990).

These devices generally have a fast frequency response (Schettini *et al.*, 1971; Honda, 1984; Overweg-Plandsoen, 1990). A drawback of the strain gauge transducers, is their possible temperature dependency (Schettini *et al.*, 1971; Honda, 1984). During measurement, energy dissipated in the gauges can alter the temperature of the transducer, resulting in a pressure drift. Within the RTT, little energy is dissipated inside the sensor, and this has a positive effect on the thermal stability of the device.

In both techniques, the wiring between the sensor and the impedance measuring device is very flexible; they are, therefore, less sensitive to motion artefacts.

According to Leggate and Minns (1991), an ideal pressure transducer should have a flat frequency response from zero up to about 30 Hz. Additionally, the relationship with the actual ICP should be linear. It should be sensitive and not influenced by thermal changes.

The indirect (pneumatic) AFP measurement devices cannot fulfil the frequency response requirement. A direct telemetric measuring device, the RTT, is therefore used in this study. The RTT allows in situ baseline correction, and the positioning of the sensor to the fontanelle is such that the application pressure does not interfere with the actual measured AFP. According to previous studies, the RTT has a frequency response that exceeds 50 Hz, which allows for AFP pulse wave analysis. Furthermore it has good long-term stability, is accurate and has a relatively low thermal instability (De Jong *et al.*, 1982; Maas and De Jong, 1986; Overweg-Plandsoen, 1990). Barometric pressure changes are automatically compensated for (Maas, 1985). Furthermore, the transducer has been developed from an epidural method. It is impermeable to water, and will not be affected by perspiration of the skin (De Jong *et al.*, 1979; Maas, 1985).

However, using the RTT in hydrocephalic infants, we encountered certain drawbacks, such as variable zero drifts and calibration inconsistencies. Previous studies could not explain these findings. The aim of the present study was therefore, to reassess the physical qualities of the RTT and to evaluate its validation by relating the measured AFP to the actual ICP, represented by the intraventricular pressure (IVP). In order to be able to interpret future AFP measurements obtained with the RTT in clinical practice, the data variation in different circumstances was examined. The discussion suggests a measurement protocol guaranteeing maximum accuracy.

Materials and Methods

The Rotterdam Teletransducer

The RTT is composed of a resonator and an electromagnetic coupled impedance measurement device. The resonator consists of a passive coil capacitor system enclosed within a piston. The location of the capacitor is such, that one of the plates forms the flat top of the piston. Changes in pressure applied to the top of the piston, influence the value of the capacitor and thus the resonance frequency. This is a linear relationship.

The piston is rotated manually into the thread of a light weight perspex adaptor (*Figure 1*), which rests on the skin, overlying the bony structures adjacent to the fontanelle. It is kept in place by means of rubber bands.

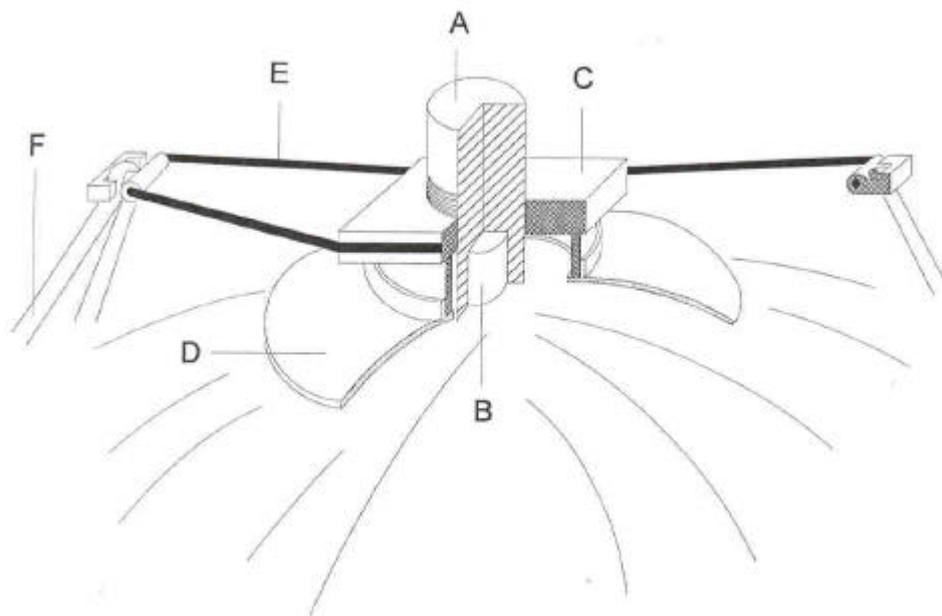


Figure 1. Mechanical construction of the RTT fixation frame and piston. A: piston; B: transducer; C: perspex body; D: adaptor fixation plate; E: loading spring; F: rubber band.

Accurate depth positioning of the piston is essential. The pressure depth curve (PD-Curve) is used to adjust the piston to the fontanelle (Plandsoen *et al.*, 1986). This curve is produced by uniformly rotating the piston into the thread of the adaptor. A characteristic plateau occurs in the PD-Curve when the top of the piston is coplanar with the fontanelle. Optimal depth positioning of the piston is at a point halfway along the plateau (Plandsoen *et al.*, 1986). The occurrence of the plateau on the PD-Curve is independent of the operator, provided the insertion is performed at a slow constant rate. Hence, the depth ascertained using the PD-Curve is largely intra- and interobserver independent and guarantees reproducible AFP measurements (De Jong *et al.*, 1984b). The size and state of the fontanelle do however, have a great influence on the quality of the measurement.

Evaluation of the RTT

The most important physical modalities were reviewed when evaluating the performance of the RTT. This was done both *in vitro* and *in vivo* experiments. *In vitro*, the RTT was tested using a specially developed calibration device. *In vivo*, several AFP and intraventricular pressure (IVP) measurements were carried out simultaneously.

In vitro measurements

A sensitive calibration device was constructed, consisting of a pressure chamber with fixed walls except for an area covered with a Latex membrane (*Figure 2*). The piston can be positioned on this membrane by means of a mounting device.

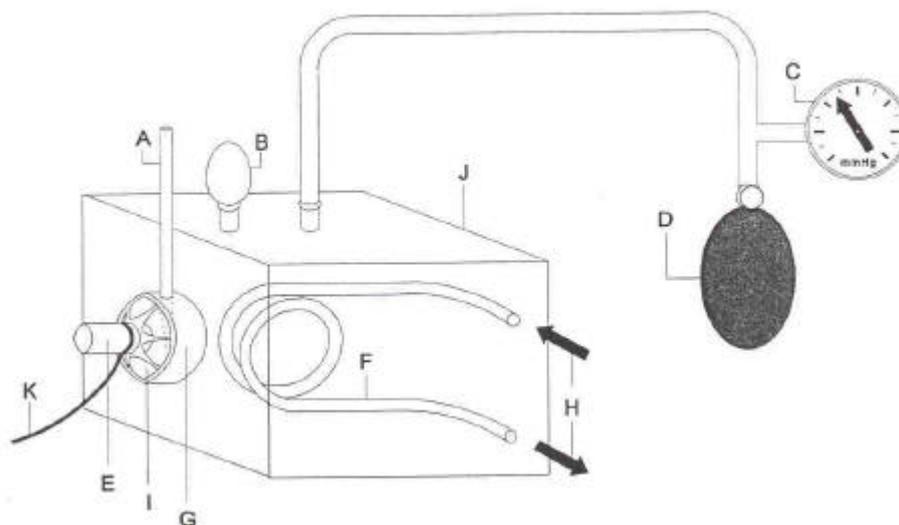


Figure 2. Calibration device. A: thermometer; B: expansion unit; C: calibrated manometer; D: rubber inflation balloon; E: piston; F: heating unit; G: mounting device; H: hot water inlet/outlet; I: membrane; J: calibration device; K: electrical wire to impedance measurement device.

Pressure on the membrane of the calibration device can be verified with the UTAH Medical VERI-CAL[®] pressure transducer tester, to an accuracy of 0.1 mmHg. The pressure measured by the RTT was recorded on an IBM compatible personal computer using the Metrabyte DAS16[®] 12 bit analogue- to-digital converter. Multichannel data acquisition recording software (MKR[®]) was used for data storage.

The in vitro measurements of the RTT can be divided into two parts. First of all the performance of the RTT was examined under ideal laboratory conditions. Secondly, as several clinical factors may have a negative effect on the accuracy of the calibration, these were investigated in simulated clinical situations.

Laboratory conditions

Dissipation of energy by electrical components increases the temperature inside the measurement device. This influences the (electrical) characteristics of the RTT and its performance. The *thermal stabilization time*, defined as the time needed for the output of the system to stabilize after being switched on, has to be specified. After calibration, the pressure measured by the RTT was registered over a period of 5 hours. The membrane of the calibration device was at room temperature (21 °C).

In addition, prior to the measurement, the RTT has to be calibrated. Performance of the RTT was investigated using a stabilized system, with the insertion depth of the transducer set at the plateau of the PD-Curve. *Calibration* was performed at 0.0 and 40.0 mmHg. After each measurement, gain and offset were randomly altered, prior to readjusting the piston to the membrane and to the subsequent recalibration.

Simulated clinical conditions

In clinical measurements, the RTT is calibrated on the membrane (21 °C) of a calibration device and subsequently transferred to the fontanelle (37 °C). When electrical qualities of the resonator show *temperature dependency*, measurement errors are possible. In order to determine temperature dependency, the resonator was calibrated, after thermal stabilization, on the membrane at room temperature (21 °C). Next, the temperature of the membrane was increased to 37 °C and an AFP measurement repeated without recalibrating the RTT.

In clinical measurements, the piston with the transducer is moved from the calibration device and readjusted to the fontanelle. This could influence calibration qualities and thus the accuracy of the measurement. To assess this, the piston was put into position on the calibration device using the PD-curve and a calibration was performed. After removing the piston from the membrane and subsequently reinserting it in the mounting frame, the offset was adjusted to 0.0 mmHg just prior to the point at which the piston touches the membrane. The relationship between generated and measured pressure was subsequently determined, with the membrane at room temperature (21 °C).

In vivo measurements

The method of measuring the AFP must always guarantee that the results bear a close relation to the actual ICP. To validate the RTT, several longterm measurements of AFP and IVP were performed simultaneously, in order to verify the relationship between the pressure measured by the RTT and the actual IVP. The IVP is used as a standard reference for the ICP. For the IVP measurements, a ventricular drain was connected to an HP1290A[®] probe and HP78205D[®] pressure unit. During the measurement, the child was in a supine position. AFP and IVP were continuously recorded on a computer for several hours and correlated off-line.

Results

In vitro measurements

Laboratory conditions

Thermal stabilization time. The results show a rapid decrease in measurement output during the first hour, and after 3 hours there was no output drift. Thermal stabilization time is, therefore, considered to be 3 hours. The difference between measured pressure at the start and three hours later is at least 3 mmHg.

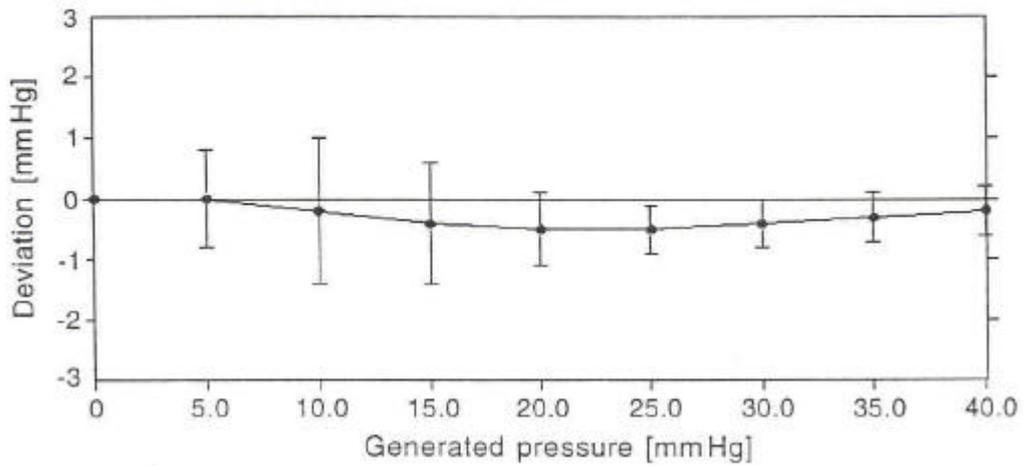
Calibration. The results of 90 calibration measurements (*Figure 3a*) show an overall mean pressure difference of -0.3 mmHg. The largest mean pressure deviation occurs between 10 and 20 mmHg, with maximum deviation limits (Mean \pm 2•SD) ranging from -1.4 up to 1.0 mmHg.

Simulated clinical conditions

Membrane temperature. The results show that the difference in membrane temperature during measurement (37 °C), compared to the membrane temperature during calibration (21 °C), has no significant effect on the AFP measurement.

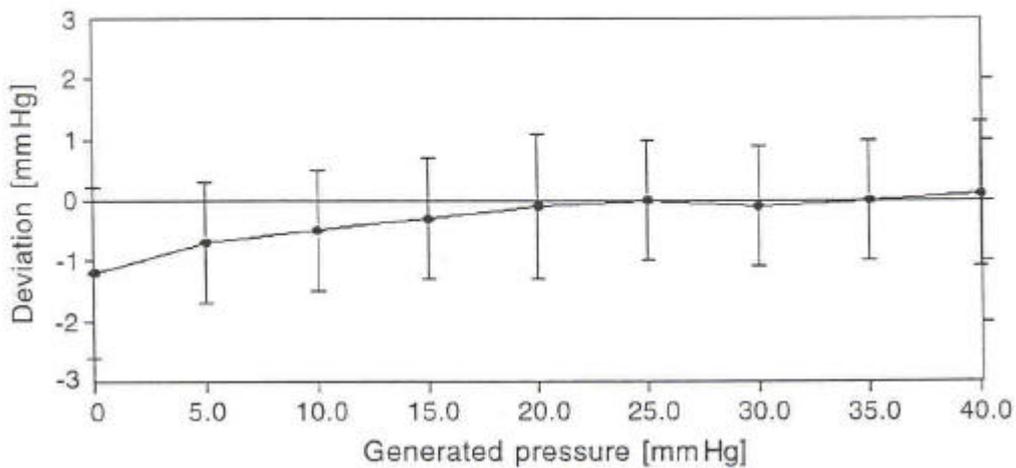
Simulation of transducer manipulation in clinical practice. The results show that the manipulation of the piston and subsequent zero adjustment apparently have an effect on the accuracy of the measurement (*Figure 3b*). Below 20 mmHg, the deviation between measured pressure and generated pressure increases, as the generated pressure decreases. The deviation limits (Mean \pm 2•SD) range from -2.6 up to 1.3 mmHg.

M	:	0.0	0.0	-0.2	-0.4	-0.5	-0.5	-0.4	-0.3	-0.2
SD	:	0.0	0.4	0.6	0.5	0.4	0.2	0.2	0.2	0.2
95% c.i.:	M +/-	0.0	0.3	0.4	0.3	0.2	0.1	0.1	0.1	0.1
95% p.i.:	M +/-	0.1	1.0	1.3	1.1	0.8	0.5	0.4	0.4	0.4



a

M	:	-1.2	-0.7	-0.5	-0.3	-0.1	-0.0	-0.1	-0.0	0.1
SD	:	0.7	0.5	0.5	0.5	0.6	0.5	0.5	0.5	0.6
95% c.i.:	M +/-	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
95% p.i.:	M +/-	1.6	1.3	1.2	1.3	1.4	1.3	1.2	1.2	1.4

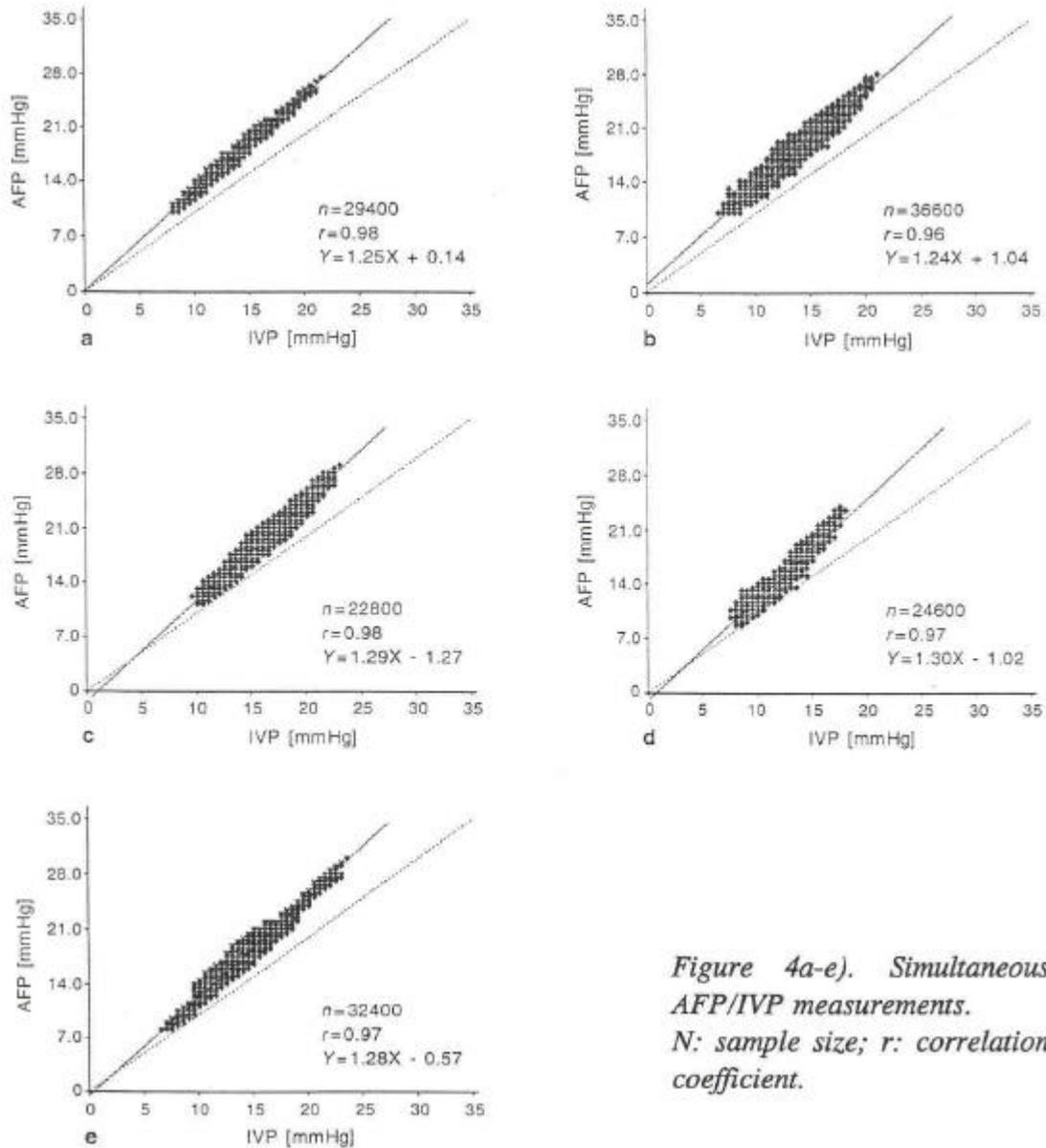


b

Figure 3. Deviation between generated pressure and measured pressure. For each class of generated pressure $N=10$. Numerically presented: mean (M), standard deviation (SD), 95% confidence interval ($c.i.$) for the mean, 95% prediction interval ($p.i.$) for new observations (Neter et al., 1988). Graphically presented: mean $\pm 2 \bullet SD$. a: calibration; b: manipulation of the transducer and subsequent zero adjustment.

In vivo measurements

The measurements show high correlations (r : 0.96 - 0.98) between the AFP measured with the RTT and the IVP (*Figure 4*). AFP measurements exceed the IVP values. The difference between AFP and IVP values increases with increasing pressure. By means of linear curve-fitting, the slope of each curve was calculated, and found to vary between 1.24 and 1.30.



*Figure 4a-e). Simultaneous AFP/IVP measurements.
N: sample size; r: correlation coefficient.*

Discussion

This study reassessed the physical qualities of the Rotterdam Teletransducer (RTT) in order to allow performance of reliable pressure measurements for clinical interpretation. The value of the AFP measurements for determining the ICP depends on the relationship between these two variables. The main advantages of the RTT, as a fontanometer, are the special fixation frame of the transducer, which means that the pressure applied by the frame does not interfere with the measured pressure, and the ability to perform bedside calibration. Additionally, the fast dynamic response of the RTT allows for ICP pulse wave analysis.

When using the RTT in AFP measurement, proper depth setting of the piston is of primary importance. This is accomplished using the pressure depth curve (PD-Curve) (Plandsoen *et al.*, 1986). If the depth setting procedure is performed accurately, AFP measurements are reproducible and the interobserver error is very small.

The physical qualities of the RTT were investigated in three different ways: (1) *in vitro* measurements under ideal laboratory conditions, (2) *in vitro* measurements under simulated clinical circumstances, and (3) several simultaneous *in vivo* AFP/IVP measurements.

1. Under ideal laboratory conditions, the warming-up period (thermal stabilization time) after switching on was determined, and found to be at least 3 hours. Insufficient thermal stabilization can result in the measured pressure being underestimated by as much as 3 mmHg.

After thermal stabilization, the system has to be calibrated. Calibration is investigated using a specially developed calibration device. After calibration, the results show a maximum prediction interval of ± 1.3 mmHg. The maximum inaccuracy of pressure measurement, is therefore 1.5 mmHg. This is in accordance with previous estimates which state an inaccuracy of less than ± 2 mmHg (Overweg-Plandsoen, 1990). Performing calibration on more than 2 points (0.0 and 40.0 mmHg) did not increase accuracy.

2. In clinical practice, the temperature of the fontanelle differs from that of the calibration membrane. The results of the experiments indicate that this temperature difference does not contribute significantly to the measurement error. However, after sufficient thermal stabilization, calibration and offset correction, manipulation of the piston, such as moving it from the calibration device to the fontanelle, appears to have a considerable effect on the accuracy of the measurement. The results show a maximum prediction interval of ± 1.6 mmHg. Manipulation of the piston therefore, after calibration, increases the maximum inaccuracy of pressure measurement to 2.8 mmHg. 3. The clinical relevance of measurements with the RTT is determined by the relationship between AFP and ICP (or IVP). Simultaneous measurements show correlations between AFP and IVP varying from 0.96 to 0.98. In all these measurements, as pressure increases, AFP exceeds IVP values (offset of 3 to 4 mmHg). This phenomenon has been recognized in the literature (Schettini *et al.*, 1971; Jørgensen and Riishede, 1972; Sundbärg and Nornes, 1972). Suggested explanations are: the effect of the combination of tissues overlying the fontanelle; stretching forces of the skin exerted on the transducer membrane; and the difference in pressure between the subarachnoid space and the brain itself (Sundbärg and Nornes, 1972).

From the experimental results of the present study, it can be concluded that if certain steps are not taken, a considerable measurement error can occur. The following measurement protocol, should therefore be carried out to ensure maximum accuracy, assuming no ossification and a sufficient size (preferably no smaller than 2 x 2 cm) of the fontanelle. First of all, allow a stabilization period of at least 3 hours. Then adjust the piston to the calibration device on the plateau of the PD-curve, and subsequently perform a calibration on the calibration device. Finally, move the piston from the calibration device to the fontanelle and adjust offset (zero), just prior to the moment at which the piston touches the skin.

Conclusion. The RTT has been proved to be an accurate and reliable device for determining the ICP by measuring the AFP, if extended operating procedures are observed. However, hardware improvements to reduce thermal stabilization time and improve the gain and offset adjustment procedures, might increase its reliability even further.

CHAPTER 3

THE RELATIONSHIP BETWEEN ANTERIOR FONTANELLE PRESSURE MEASUREMENTS AND CLINICAL SIGNS IN INFANTILE HYDROCEPHALUS

Abstract

The treatment of choice in progressive hydrocephalus is cerebrospinal fluid (CSF) drainage, to decrease elevated intracranial pressure (ICP). Defining the right moment for surgical intervention however, in a hydrocephalic infant, based on clinical signs alone, can be a difficult task. Clinical signs of raised intracranial pressure (ICP) are known to be unreliable and sometimes even misleading.

In this present study, the relationship between long-term AFP measurements and clinical signs, was investigated in 37 infants with hydrocephalus. The decision as to whether or not to operate was based on clinical signs alone, AFP values were not taken into account. There was an overall difference, between the not-operated and operated (pre-operative) group, and also between the pre-operative and postoperative group, regarding both the AFP measurements and clinical signs. Almost all of the pre-operative AFP values were increased. The direct correlation (ϕ) between the individual clinical signs and the actual AFP levels however, was low for most of the signs ($\phi = 0.15 - 0.41$). The clinical sign, 'tense fontanelle', showed the best correlation with the AFP levels ($\phi = 0.75$). Furthermore, using logistic regression analysis, no combination of clinical signs could be found, to provide a reliable prediction of the AFP.

The relationship between the AFP pressure variables and clinical signs was also examined. The pathological A-waves occurred only in the presence of raised (baseline) AFP, a situation in which considerably more frequent B-waves were observed as well.

It was concluded that, clinical signs of raised ICP in infantile hydrocephalus are not very reliable and ICP monitoring can therefore, provide valuable information on intracranial dynamics, in patients with dubious neurological manifestations of progressive hydrocephalus.

Introduction

Continuous monitoring of intracranial pressure (ICP) can be useful in the observation, diagnosis, and treatment of infants with intracranial disorders such as hydrocephalus, head injury, asphyxia, as well as infectious, metabolic and toxic encephalopathies (Mann and Punt, 1986). Due to the risk of serious complications, invasive measuring devices are not as commonly used in infants as in adults. To minimize the risks of ICP monitoring, a simple non-invasive method for measuring the ICP, using the applanation principle, was developed by Wealthal and Smallwood (1974). A reliable technique, known as the Rotterdam Teletransducer (RTT), which uses the same principle, has been described previously (De Jong *et al.*, 1984b; Overweg-Plandsoen, 1990; Peters *et al.*, 1995).

One of the problems in evaluating ICP data in infants however, is the uncertainty about defining "normal" ICP, which changes with the natural development of infants (Welch, 1980). A wide range of normal ICP values, measured both invasively and non-invasively, in infants has been reported (Kaiser and Whitelaw, 1986; Minns *et al.*, 1989; Anegawa *et al.*, 1991a). To add to this, there is little information available on ICP measurements in infants, in relation to clinical signs and outcome. Furthermore, little is known about intracranial dynamics, partially reflected in the ICP waveform, in infants at different ages. The ICP waveform observations in adults, carried out by Lundberg (1960), are not completely applicable for infants. Abnormal ICP registrations in hydrocephalic infants, where pressure waves seem to be a pathological phenomenon, due to decreased ability for spatial compensation, have often been reported (Chawla *et al.*, 1974; Di Rocco *et al.*, 1975; Symon and Dorsch, 1975; Pierre-Kahn *et al.*, 1976; McCullough, 1980; Anegawa *et al.*, 1991b).

In progressive hydrocephalus, cerebrospinal fluid (CSF) drainage is the treatment of choice to decrease elevated ICP and maintain intracranial dynamics, especially the cerebral perfusion pressure (CPP: mean arterial blood pressure - ICP), within physiological limits (CPP: > 30 mmHg in neonates; > 50 mmHg in children < 5 yrs of age), in order to avoid secondary cerebral damage. Evaluating the rate at which the hydrocephalic process progresses and defining the right moment for shunt implantation however, is a difficult task, based on the current most common clinical signs. Shunt complications, especially shunt infections, are quite common, and can cause serious morbidity and deterioration of the ICP. Unnecessary implantation, therefore, should be avoided and early clinical detection of malfunction is very important. Clinical signs or symptoms of raised ICP are known to be non-specific and often unreliable (Kaiser and Whitelaw, 1987; Di Rocco *et al.*, 1989; Kirkpatrick *et al.*, 1989). To date, no study has been performed, that clearly describes the combination of clinical signs, that provides the most reliable prediction of elevated ICP and deteriorating intracranial compliance. The clinical management of childhood hydrocephalus, thus remains uncertain.

Proper treatment of elevated ICP levels is crucial in progressive hydrocephalus, and the present study on the value of non-invasive ICP measurements was, therefore, conducted. The purpose of this study was to investigate (1) the relationship between the treatment decision

whether to operate or not and clinical signs or anterior fontanelle pressure (AFP); (2) the relationship between clinical signs and AFP and (3) the relationship between clinical signs and AFP waveform characteristics, in long-term measurements.

Materials and Methods

Materials

Using a well-defined protocol for extensive observations of hydrocephalic infants, 37 patients (19; 18) were selected and studied by means of both clinical examination, including imaging techniques, and anterior fontanelle pressure measurements. The aetiology of hydrocephalus involved is shown in *Table 1*. Hydrocephalus was diagnosed by means of CT or MRI (Philips Gyroscan[®]) criteria. Patients with a combination of hydrocephalus with structural cerebral lesions, such as an intracerebral tumor, were excluded. Based on clinical observations and imaging criteria alone, infants were divided into two groups: not-operated and operated (implantation of a ventriculoperitoneal shunt). In none of the patients AFP values were taken into account in deciding whether or not CSF drainage was appropriate. All patients were followed-up according to the protocol, i.e. pre-operatively, 1 week postoperatively, 6 weeks postoperatively, 3 months postoperatively and 6 months postoperatively, the protocol being restarted whenever a shunt revision was performed. The patients who were not operated, because of suspected compensating hydrocephalus, were followed-up at monthly intervals, for up to 6 months after the initial evaluation. At every point in the follow-up, all short-term clinical signs (*Table 2*) were scored (sunsetting and distal diplegia were scored at 6 weeks intervals only), in order to evaluate the shunt function or the progression of the hydrocephalic process, whilst the AFP was measured, whenever possible (open fontanelle), at the same time. A total of 207 clinical follow-up studies, with 136 long-term AFP measurements were evaluated. 37 pre-operative AFP measurements, including 16 shunt revisions in 8 patients, were examined. Shunt dysfunction was caused by infection, mechanical malfunction, disconnection or malposition of the shunt.

Methods

The state of the infant during AFP measurements was scored according to the Beintema and Precht criteria (Beintema and Precht, 1968); measurements with too many artefacts (state 4 and 5) were excluded. A continuous

Table 1. Patient characteristics.

	♂	♀
Sex distribution	19	18
Mean age (months) [SD]	3.8 [3.3]	2.2 [3.3]
Aetiology of hydrocephalus		
aqueductal stenosis	6	5
associated with spina bifida	3	7
post haemorrhagic hydrocephalus	5	2
post meningitic hydrocephalus	1	2
idiopathic	4	2
Type of hydrocephalus		
obstructive hydrocephalus	13	13
communicating hydrocephalus	5	4
external hydrocephalus	1	1

non-invasive measurement technique of blood pressure in infants was not available at the time of this study. Exact calculations of the cerebral perfusion pressure, were therefore not possible. Blood pressures were evaluated before and after the AFP measurements and had to be within accepted physiological limits. All AFP measurements were carried out over a minimum period of 3 hours (range: 3 - 30 hours). The Rotterdam Teletransducer (RTT), which is known to be a reliable technique for anterior fontanelle pressure measurements, with a close relationship ($r: 0.96 - 0.98$) between the AFP and the intraventricular pressure (Peters *et al.*, 1995), was used. Calibration of the RTT was performed using a specially developed calibration device.

A high resolution recording computer system was constructed and signals were sampled, through a DAS16 analogue to digital converter (12 bit, Keithley Instruments), using a multichannel data acquisition program. Along with the anterior fontanelle pressure (50 Hz), the ECG (100 Hz) and respiration (10 Hz) signals were recorded. Parallel to the digital recording, the signals were printed on a multichannel plotter (Gould TA2000[®]) for ICP waveform analysis. Computer analysis of the intracranial pressure data was performed, using a specially developed software program (CRANIEEL[®]).

AFP-values

AFP reference values were obtained from our own data and from another investigator's data, acquired with exactly the same equipment (Overweg-Plandsoen, 1990). These reference values are age-dependent: ≤ 1 month: 9 ± 2 mmHg; > 1 month: 11 ± 2 mmHg, and higher AFP values in this study were regarded as abnormal. It is known that the normal values acquired with the RTT are slightly higher than otherwise measured fontanelle pressure values (De Jong *et al.*, 1984b; Overweg-Plandsoen, 1990).

AFP waveform

Special attention was paid to the AFP waveform in infants. An A-wave, in infants with an open fontanelle, was defined as a sudden pressure increase over 15 mmHg above the baseline pressure, lasting more than 5 minutes (plateau), with an abrupt or sometimes gradual decline (Lundberg, 1992; Anegawa *et al.*, 1991a) (*Figure 1*). In this study the presence of A-waves was considered to be abnormal. B-waves were defined as pressure increases up to 15 mmHg above the baseline pressure, with a frequency of 3 - 4 per minute. More than 5% B-waves was considered to be abnormal (Börgeesen and Gjerris, 1987). C- and D-waves were not evaluated. Periodic pressure increase, other than A- or B-wave, was defined as an increase of no more than 15 mmHg, lasting longer than 5 minutes. The aspect of the baseline pressure, stable or unstable, was evaluated throughout each measurement.

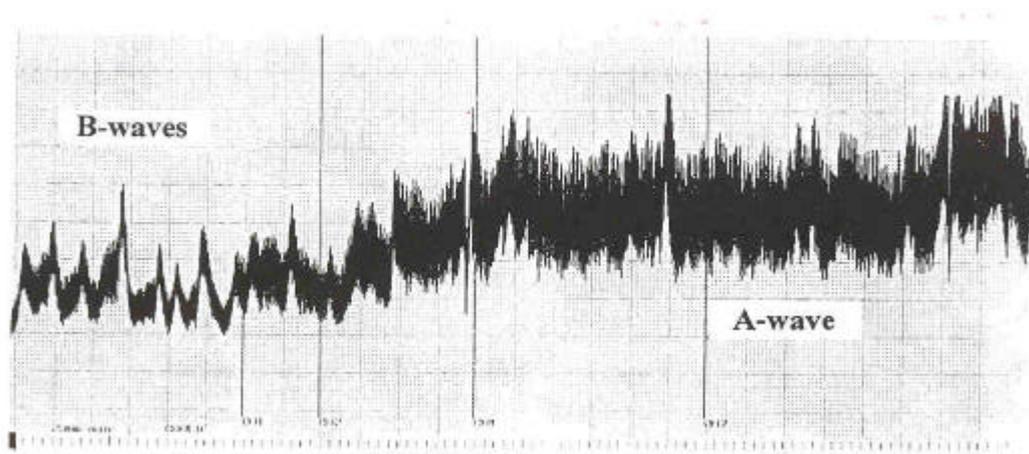


Figure 1. Anterior fontanelle pressure measurement: A-wave preceded by B-waves.

Statistical analysis

For analysis purposes, all clinical signs as well as the AFP data were coded as normal or abnormal. By using Fisher's exact test, differences in proportions of clinical signs and AFP variables were analyzed. Only *p*-values below 0.05 were considered significant. Comparisons were made between the measurements in the not-operated and operated group, between the pre-operative and postoperative measurements, and between AFP variables in measurements with a normal and abnormal mean AFP. The correlations between clinical signs and normal

or abnormal AFP values were calculated (*phi coefficient*: the degree of correlation or association between the two variables in two by two tables). Furthermore, the relationship between the AFP and the treatment decision as to whether to operate or not was investigated, along with the relationship between the individual clinical signs and the actual AFP values. In order to reveal the best possible combination of clinical signs for predicting the actual mean AFP, or an abnormal AFP value, multiple and logistic regression analyses, including all short-term clinical observations, were performed, respectively. Multiple regression analysis, applied the 'goodness-of-fit' principle and the adjusted R^2 for each combination of clinical signs was subsequently calculated.

Results

Treatment decision in relation to AFP measurements

In this study the decision to perform shunt implantation in infants with hydrocephalus was based on clinical signs alone, the AFP measurements were not taken into account.

Most of the AFP measurements (*Table 2a*) or clinical observations (*Table 2b*) in the not-operated group, i.e. patients with ultimately compensated hydrocephalus, were significantly different from the operated group, except for periodic pressure increase ($p = 0.44$), scalp vein distension ($p = 0.28$), vomiting ($p = 0.06$) and anorexia ($p = 0.15$). The effect of surgical intervention was investigated by comparing the pre-operative to the postoperative data, of patients who had undergone a successful CSF drainage procedure (*Table 3a/b*). All postoperative measurements or observations differed significantly from the pre-operative data, except for anorexia ($p = 0.18$).

The pre-operative mean AFP (mmHg) and standard deviation [SD] was 20.7 [10.1], 11.8 [3.1] postoperatively and 15.1 [3.6] in the not-operated group. The postoperative data included 12 measurements during intermittent shunt dysfunction, not requiring shunt revision. The actual postoperative mean AFP in cases of adequate shunt function, was therefore slightly less than 10 mmHg.

The evaluation of the decision to operate or not was compared to the AFP values within the different groups. In the operated group, almost all pre-operative AFP values were increased (92%), whereas 71% of the AFP measurements in the not-operated group were increased. The highest AFP values (>18 mmHg) were observed twice as often in the operated group.

The relationship between clinical signs and AFP

The correlations (*phi*) between normal or increased mean AFP and clinical signs for all measurements are presented in *Table 4*. The correlation between AFP and 'tense fontanelle' is 0.75, other signs show a poor correlation with normal or abnormal mean AFP, $phi = 0.15 - 0.41$. The relationship between the individual clinical signs and the actual AFP values is illustrated in *Figure 2*. The condition of the fontanelle showed the best relation to the height

of the AFP, although a distinct overlap between normal and tense fontanelle in relation to the AFP values was observed.

The best possible combination of clinical signs for predicting the height of the mean AFP was: tense fontanelle (as most important factor), impaired consciousness (which had a low incidence) and distal diplegia (with no spina bifida involvement). A maximally adjusted R^2 of 37% was calculated, using a multiple regression analysis, with mean AFP as the dependent variable. Application of the most important clinical signs of progressive hydrocephalus, such as abnormally increasing head circumference, tense fontanelle and sunseting, provided an adjusted R^2 of only 26% and a maximum of 32% was reached by adding 'impaired consciousness' to this multiple regression analysis.

Logistic regression analysis was applied, in order to evaluate the prediction of normal or abnormal mean AFP, by a combination of clinical variables and the results were similar to those obtained in multiple regression analysis. 'Tense fontanelle' turned out to be the most important variable and the addition of other variables had little influence on the prediction.

AFP waveform analysis

Probably not only the mean AFP, but also the different aspects of the AFP waveform are important reflections of the intracranial dynamic response. Significant differences, concerning waveform characteristics, were apparent between normal and abnormal AFP measurements (*Table 5*). The associations (*phi coefficient*) between the AFP waveform characteristics and the different clinical signs were similar, but less apparent, to the associations with normal or abnormal mean AFP. Again, the 'tense fontanelle' was best correlated with the AFP waveform variables.

A-waves were observed in 35% of the pre-operative measurements and in 24% of the measurements in the not-operated group. There were clear differences in calculated percentages of A-waves during measurements between the operated and not-operated group (*Table 6*). Only one patient showed A-waves in the postoperative measurements. No A-waves were observed in measurements with normal mean AFP. The number of B-waves (frequent: > 50%; periodic: 5 - 50%; sporadic: < 5%; no B-waves) in the AFP measurements show distinct differences between normal and abnormal AFP measurements, with the largest number of B-waves occurring in the pre-operative measurements (*Table 7*). In the not-operated group, the number of B-waves in the measurements with elevated AFP, was less pronounced. Periodic pressure increase was observed almost as often in the not-operated group with abnormal AFP measurement, as in the pre-operative abnormal AFP measurements (*Table 7*). In only one pre-operative normal AFP measurement, a periodic pressure increase was observed.

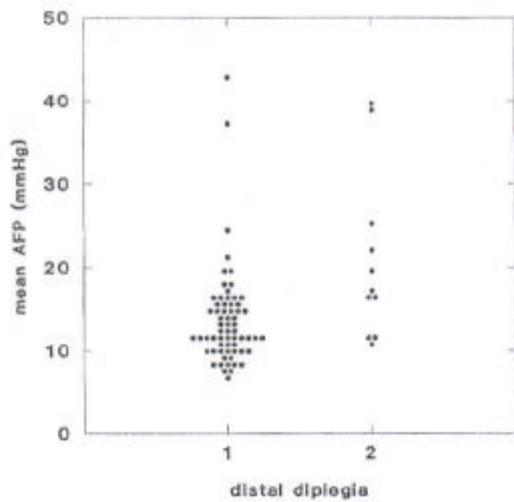
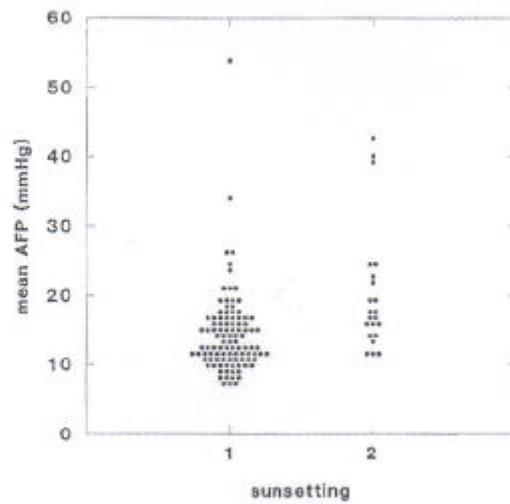
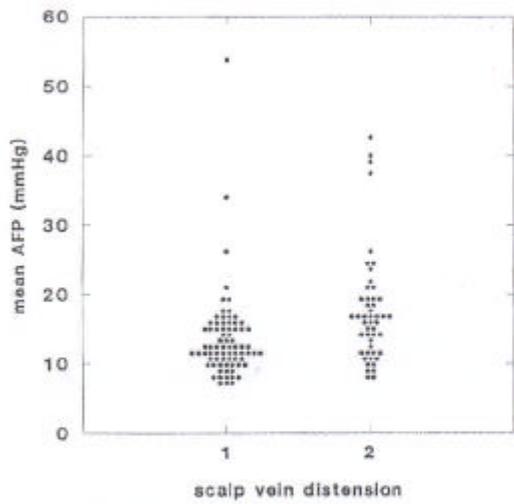
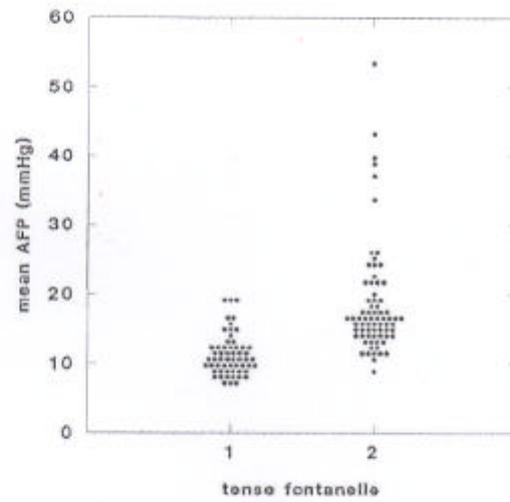
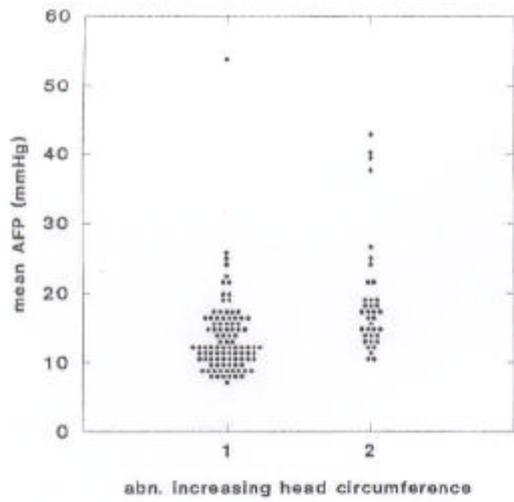


Figure 2. Relationship between the absence or presence of the individual clinical signs and the actual AFP values. (1) clinical sign absent; (2) clinical sign present.

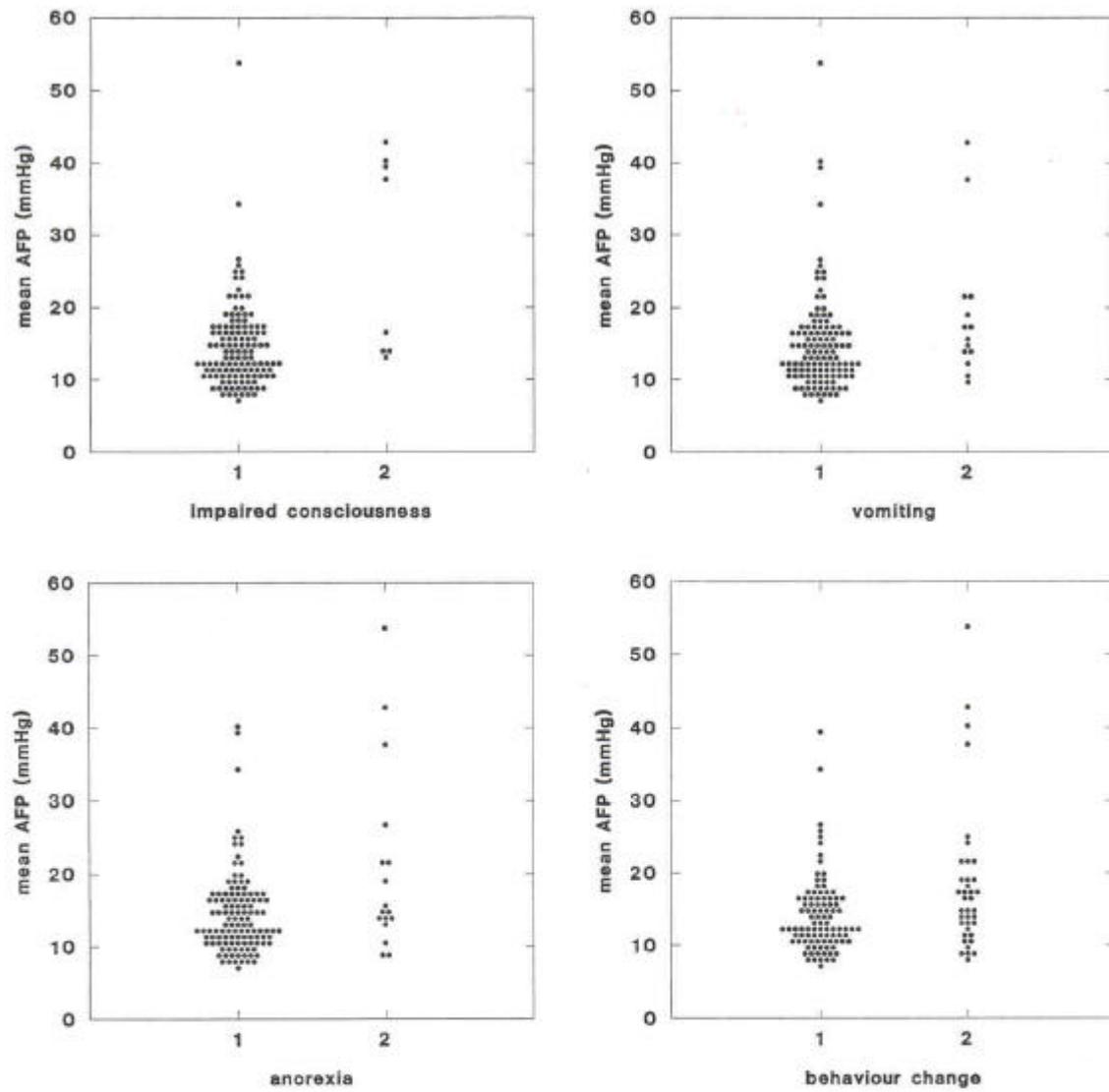


Figure 2 (continued). Relationship between the absence or presence of the individual clinical signs and the actual AFP values. (1) clinical sign absent; (2) clinical sign present.

Clinical implications of AFP measurements in childhood hydrocephalus

Of the 15 not-operated patients on entering the study, 5 were operated at a later stage, and in 3 of them, several abnormal AFP measurements were observed prior to the actual decision to operate. In 6 measurements prior to the pre-revision measurement, mean AFP was increased, indicating a progressive hydrocephalic process, at which time clinical signs were either absent or inconclusive. Thus, nine (24%) of the 37 pre-operative AFP measurements were preceded by abnormal AFP measurements. In 10 (27%) measurements, regularly monitored according to the protocol, with no obvious clinical signs of progressive hydrocephalus, in the period shortly before admission to the hospital, subsequent clinical examination suggested a shunt dysfunction and a shunt revision was necessary. In all of these measurements, mean AFP values were increased.

Discussion

Hydrocephalus is a disorder encountered in any pediatric neurological and neurosurgical practice, with an incidence of approximately 3 in 1000 live births. Management of progressive hydrocephalus entails CSF drainage, in order to decrease raised ICP and restore cerebral perfusion pressure, thereby avoiding a secondary cerebral ischaemic insult. The most frequent complication of shunt implantation is mechanical blockage, with or without infection, with increasing ICP (Leggate *et al.*, 1988). The most common clinical signs of raised ICP are often unreliable and sometimes even misleading. The most reliable indication of decreased intracranial compliance and shunt malfunction might, therefore, be best derived from long-term ICP monitoring (Leggate *et al.*, 1988). Controversial reports however, on the value of ICP and CPP monitoring in childhood hydrocephalus have been previously published (Hayden *et al.*, 1970; Di Rocco *et al.*, 1975; Vidyasagar *et al.*, 1978; McCullough, 1980; Gaab *et al.*, 1982; Colditz *et al.*, 1988; Sato *et al.*, 1988; Minns *et al.*, 1989; Anegawa *et al.*, 1991b). Furthermore, the current literature provides only limited data on the direct relationship between clinical signs and ICP, including waveform analysis, in childhood hydrocephalus. This present study is concerned with two distinct groups of hydrocephalic patients: (1) not-operated, ultimately compensated hydrocephalus, and (2) operated (primary shunt implantation or shunt revision). Comparison of both groups was based on clinical signs (abnormally increasing head circumference, tense fontanelle, scalp vein distension, sunseting, distal diplegia, impaired consciousness, vomiting, anorexia, behaviour change) and anterior fontanelle pressure measurements. The difference in clinical signs and AFP measurements between the not-operated and operated group reached significance for almost all variables. In this comparison, periodic pressure increase, scalp vein distension, vomiting and anorexia turned out to be non-specific signs. Comparison of the pre-operative and postoperative measurements revealed that only periodic pressure increase and anorexia were classified as non-specific signs.

The presence of certain clinical signs may be accompanied by normal AFP measurements and vice versa and, it is for this reason, that the correlations between each individual clinical sign and the mean AFP were calculated. These correlations were poor ($\phi = 0.15 - 0.41$), except for the 'tense fontanelle' ($\phi = 0.75$). The correlations between clinical signs and the waveform characteristics (unstable baseline pressure, A-waves, B-waves and periodic pressure increase) were even worse and provided no additional information.

It can also be concluded from the data on hydrocephalic patients, that the presence of a clinical sign such as abnormally increasing head circumference, tense fontanelle, sunsetting or loss of upward gaze, and impaired consciousness is a likely indicator of abnormal intracranial pressure. According to the multiple regression analysis however, little can be said about the approximate height of the ICP and its effect on the intracranial dynamic response, which shows large inter-individual variations in infants (Gooskens *et al.*, 1985a). Furthermore, when the same signs, with exception of the 'tense fontanelle,' are absent at clinical examination, ICP can just as often be normal as increased. Although absence or presence of the 'tense fontanelle' correlates best with normal or increased AFP, respectively, there was still a distinct overlap between the different conditions of the fontanelle and the actual AFP values. The fact that the expanding head circumference is compensatory to raised ICP and that it acts as a buffer, explains its poor relationship with the height of the AFP, although, the abnormally increasing head circumference can be an important sign of progressive hydrocephalus.

There was also a distinct difference in the occurrence of A- and B-waves between the not-operated and operated groups. The fact that A-waves occurred more frequently and more obviously in the pre-operative measurements, suggests more advanced deterioration of intracranial dynamics, with possibly unstable CPP and decreased compliance (Rosner and Becker, 1984; Sirovskiy *et al.*, 1994). No A-waves occurred in measurements with normal mean AFP and normal baseline pressure, and were very uncommon in the newborn, which has been previously described by Paraicz (1978). The relationship between REM sleep and A-waves in hydrocephalic children has been described in other reports, and has not been addressed in the present study (Di Rocco *et al.*, 1975; Pierre-Kahn *et al.*, 1976; McCullough, 1980; Whittle *et al.*, 1985; Anegawa *et al.*, 1991b; Goh *et al.*, 1992a). The pathophysiology of this phenomenon still remains the subject of discussion.

Our findings are in accordance with those of Kirkpatrick *et al.* (1989), who showed that clinical signs and symptoms in childhood hydrocephalus are often unreliable.

Uncommon clinical features of raised ICP such as neurogenic pulmonary oedema, profuse sweating (diencephalic autonomic epilepsy?), ptosis, autonomic dysfunction and neurogenic stridor (bilateral cortico-bulbar lesion) were not encountered in the present study and only two patients developed epilepsy.

Conclusion. From the measurements obtained during patient follow-up, it can be concluded that raised ICP, accompanied by few or no clinical signs, can be the only early apparent sign of progressive hydrocephalus. Raised ICP has the potential to cause cerebral damage in due course, with clinical signs only becoming obvious much later.

In selected patients with dubious neurological manifestations of progressive hydrocephalus, anterior fontanelle pressure measurements can be helpful in deciding the right moment for a CSF diversion procedure or shunt revision, because one cannot rely on clinical features alone to determine the diagnosis.

Table 2a. Comparison of anterior fontanelle pressure (AFP) measurements between not-operated and operated hydrocephalic infants.

	not-operated	pre-operative	p-value (one sided)
AFP measurements (% (no.) abnormal or present)	% (no.)	% (no.)	
mean AFP	71 (25)	92 (34)	0.02
baseline AFP	17 (6)	62 (23)	<0.001
unstable baseline pressure	43 (15)	78 (29)	0.01
A-waves	17 (6)	38 (14)	0.04
B-waves	43 (15)	81 (30)	<0.01
A-waves preceded by B-waves	100 (6)	86 (12)	
periodic pressure increase	71 (25)	76 (28)	0.44

Table 2b. Comparison of clinical observations between not-operated and operated hydrocephalic infants.

	not-operated	pre-operative	p-value (one sided)
Clinical signs (% (no.) present)	% (no.)	% (no.)	
abnormally increasing head circumference	22 (12)	61 (26)	<0.001
tense fontanelle	68 (25)	90 (38)	<0.01
scalp vein distension	40 (18)	49 (19)	0.28
sunsetting	11 (6)	43 (18)	<0.001
distal diplegia*	5 (2)	35 (10)	<0.01
impaired consciousness	0 (0)	16 (7)	<0.01
vomiting	8 (4)	20 (9)	0.06
anorexia	6 (3)	14 (6)	0.15
behaviour change (including irritability)	13 (7)	54 (23)	<0.001

* spina bifida excluded

Table 3a. Comparison between pre-operative and post-operative measurements of anterior fontanelle pressure (AFP) in hydrocephalic infants.

	pre-operative	post-operative	p-value (one sided)
AFP measurements (% (no.) abnormal or present)	% (no.)	% (no.)	
mean AFP	92 (34)	26 (17)	<0.001
baseline AFP	62 (23)	11 (7)	<0.001
unstable baseline pressure	78 (29)	30 (19)	<0.001
A-waves	38 (14)	6 (4)	<0.001
B-waves	81 (30)	31 (20)	<0.001
A-waves preceded by B-waves	86 (12)	75 (3)	
periodic pressure increase	76 (28)	55 (35)	0.03

Table 3b. Comparison between pre-operative and postoperative measurements of clinical signs in hydrocephalic infants.

	pre-operative	post-operative	p-value (one sided)
Clinical signs (% (no.) present)	% (no.)	% (no.)	
abnormally increasing head circumference	61 (26)	4 (4)	<0.001
tense fontanelle	90 (38)	21 (13)	<0.001
scalp vein distension	49 (19)	18 (18)	<0.001
sunsetting	43 (18)	6 (6)	<0.001
distal diplegia*	35 (10)	7 (4)	<0.01
impaired consciousness	16 (7)	1 (1)	<0.001
vomiting	20 (9)	2 (2)	<0.001
anorexia	14 (6)	7 (8)	0.18
behaviour change (including irritability)	54 (23)	16 (18)	<0.001

* spina bifida excluded

Table 4. Correlation (ϕ) between clinical signs and mean anterior fontanelle pressure (AFP) in hydrocephalic infants.

	All measurements		ϕ
	normal AFP	abnormal AFP	
Clinical signs (% (no.) present)			
abnormally increasing head circumference	7 (4)	43 (33)	0.41#
tense fontanelle	11 (6)	87 (66)	0.75#
scalp vein distension	23 (13)	46 (36)	0.30#
sunsetting	2 (1)	29 (21)	0.35#
distal diplegia*	8 (3)	21 (8)	0.17
impaired consciousness	0 (0)	11 (8)	0.22
vomiting	5 (3)	14 (11)	0.15
anorexia	5 (3)	18 (14)	0.19
behaviour change (including irritability)	16 (9)	38 (29)	0.25

$p < 0.001$

AFP	not-operated		pre-operative		post-operative	
	norm.	abn.	norm.	abn.	norm.	abn.
Clinical signs (no. absent/present)						
abnormally increasing head circumference	8/1	18/8	1/2	10/23	45/1	15/2
tense fontanelle	7/2	3/22	1/2	1/33	39/1	6/11
scalp vein distension	6/3	11/11	1/2	13/18	36/8	8/7
sunsetting	9/0	20/5	2/1	16/15	39/0	16/1
distal diplegia*	7/1	15/0	1/2	13/8	25/0	3/0
impaired consciousness	9/0	26/0	3/0	26/7	46/0	16/1
vomiting	9/0	23/3	1/2	27/7	45/1	16/1
anorexia	8/1	24/2	3/0	24/10	44/2	15/2
behaviour change (including irritability)	8/1	22/4	2/1	14/19	39/7	11/6

* *spina bifida excluded*

Table 5. Anterior fontanelle pressure (AFP) analysis: comparison between normal and abnormal AFP (mmHg), regarding the AFP waveform characteristics.

	AFP normal	AFP abnormal	p-value (one sided)
no. measurements	59 (43%)	77 (57%)	
mean age (months) [SD]	4.6 [3.4]	4.3 [3.2]	
no. operations (%)	3 (5%)	34 (44%)	<0.001
AFP range	7.0 - 13.0	11.4 - 53.6	
increased baseline pressure (%)	0 (0%)	58 (75%)	<0.001
unstable baseline pressure (%)	9 (15%)	56 (73%)	<0.001
A-waves (%)	0 (0%)	23 (30%)	<0.001
no. A-waves/h	-	0.5 - 2.0	
mean duration (min.) [SD]	-	11 [2.8]	
range (min.)	-	7 - 15	
mean height (mmHg) [SD]	-	40 [12]	
range (mmHg)	-	27 - 76	
mean pulsation amplitude [SD]	-	14 [4.8]	
range (mmHg)	-	7 - 25	
B-waves (%)	8 (13%)	57 (74%)	<0.001
A-waves preceded by B-waves	-	21 (91%)	
Periodic pressure increase (%)	23 (40%)	65 (85%)	<0.001
no. periodic pressure increases/h	0.5 - 2.0	0.5 - 3.5	
mean duration (min.) [SD]	7 [2.5]	12 [6.8]	

Table 6. Anterior fontanelle pressure (AFP) waveform analysis: A-waves.

	not-operated		operated	
mean age [SD] (months)	4.1	[1.5]	5.7	[2.1]
mean AFP [SD] (mmHg)	18.7	[3.0]	27.2	[11.7]
rate (%) of A-waves [SD] (percentage of measurement)	12.9	[8.0]	20.4	[11.0]
mean height of A-wave [SD] (mmHg)	32.0	[4.6]	45.2	[13.5]
mean pressure pulse ampl. [SD] (mmHg)	11.4	[2.9]	15.2	[5.5]
no. of B-waves preceding A-wave [SD]	3.8	[3.1]	5.1	[4.6]

Table 7. Anterior fontanelle pressure (AFP) waveform analysis: B-waves and periodic pressure increase.

AFP	not-operated		operated*	
	normal	abnormal	abnormal	
mean age [SD] (months)	3.9	[3.6]	4.3	[3.1]
mean AFP [SD] (mmHg)	10.8	[1.3]	16.9	[2.7]
B-waves:				
frequent (%)	0	20	50	
	> 10	> 56	> 82	
periodic (%)	10	36	32	
sporadic (%)	30	40	15	
	> 90	> 44	> 18	
no B-waves (%)	60	4	3	
Periodic pressure increase (%)	30	86	77	
mean duration (min.)	6.2	11.5	14.5	

Amount of B-waves in measurement: frequent: >50%; periodic: 5-50%; sporadic: <5%.
 * in only 3 pre-operative measurements the mean AFP was normal, therefore, no mean values were calculated.

CHAPTER 4

THE VALUE OF TRANSCRANIAL DOPPLER INDICES IN PREDICTING RAISED INTRACRANIAL PRESSURE IN INFANTILE HYDROCEPHALUS

A study with review of the literature

Abstract

Cerebral haemodynamic changes in infants with progressive hydrocephalus have been studied with the transcranial Doppler (TCD) technique. Several authors have referred to the correlation between the haemodynamic changes and increased intracranial pressure (ICP). Despite conflicting conclusions on the value of Pulsatility Index (PI) and Resistance Index (RI) measurements, for monitoring infantile hydrocephalus, these are the pulsatility indices most commonly used for this purpose. Although clinical signs of raised ICP are highly variable and unreliable in infants, assumptions have been made in most of the studies about the presence of elevated ICP on the basis of the patient's clinical state. Few studies have reported on actual ICP values however, and a direct relationship between ICP and TCD changes has never been adequately demonstrated. In the present study, this relationship was investigated in long-term simultaneous TCD/ICP measurements, in an attempt to develop a non-invasive method for monitoring the effect of ICP on intracranial haemodynamics. Two groups of data sets were established. Group I consisted of pre- and postoperative (shunt implantation) TCD/ICP measurements. Group II were long-term simultaneous TCD/ICP measurements, showing significant ICP variations. In most of the postoperative measurements, there was a decrease in the average PI and RI values. The correlation between PI or RI and ICP in the long-term simultaneous measurements however, was generally poor. The risk of obtaining false positive or false negative PI or RI values in short-term measurements was also demonstrated. It can be concluded from our results, besides the wide range of reference values for the Doppler indices and extracranial influences upon them, that the present Doppler indices are inadequate for monitoring the complex intracranial dynamic responses in patients with raised ICP.

Introduction

Increasing clinical use has been made of Doppler ultrasonography as a non-invasive method of assessing cerebral haemodynamic changes in infants and children with hydrocephalus, since Hill and Volpe (1982) first reported an increase of the pulsatility of the cerebral arterial flow velocity waveforms in 11 hydrocephalic children. Since then, Doppler studies, using either duplex scans through the anterior fontanelle or transcranial Doppler (TCD) investigations, have reported varying effects on waveform pulsatility and variable contributions of systolic peak flow velocity (SPFV) as well as end-diastolic flow velocity (EDFV) to pulsatility changes. Assumptions were made in most studies regarding the presence or absence of raised intracranial pressure (ICP) on the basis of the patient's clinical state. However, clinical signs and symptoms of raised ICP are highly variable and unreliable in infants (Kirckpatrick *et al.*, 1989). Few studies reported actual ICP values in their patients, despite the fact that all examined the role of dynamic Doppler investigations in predicting which patients would be most likely to benefit from shunt implantation or revision.

Literature review and study aim

The Gosling Pulsatility Index (PI) (Gosling and King, 1974) and Pourcelot Resistance Index (RI) (Pourcelot, 1974) are the two most commonly employed pulsatility indices in hydrocephalic patients. Both indices are ratios, designed to minimize the error in estimating the true velocity as a result of a varying angle of insonation. This may be especially important in hydrocephalus as vascular anatomy may be significantly distorted by ventricular enlargement (Finn *et al.*, 1990).

Several studies describe the relationship between ICP and arterial cerebral blood flow velocity. Seibert *et al.* (1989) used an animal model of hydrocephalus measuring the ICP directly, using a fiberoptic monitor (Camino[®]), with simultaneous Doppler recordings; their findings suggested a direct correlation between ICP, cerebral perfusion pressure (CPP) and RI. Horikawa (1991) also reported a direct relationship between increased pulsatility and raised anterior fontanelle pressure.

Direct ICP measurements by Chadduck *et al.* (1991) suggest a reliable linear relation between ICP and RI, using TCD. Goh *et al.* (1992b) also found a reliable correlation between ICP and RI for children of different age groups. Estimating the intraventricular pressure by tapping the shunt reservoir, Pople *et al.* (1991) found a significant correlation with the PI.

The relationship between ventricular dilatation and pulsatility has also been discussed in the literature. Several studies suggest that stable ventriculomegaly is associated with normal pulsatility (Deeg *et al.*, 1988; Anderson and Mawk, 1988; Norelle *et al.*, 1989; Huang and Chio, 1991). Hill and Volpe (1982) concluded that ventriculomegaly was a more critical factor than raised ICP in the pathogenesis of impaired flow velocity. Lui *et al.* (1990) concurred with these findings, reporting an increasing RI with increasing ventricular dilatation. Absence of diastolic flow velocity however, also occurred in two infants with only moderate ventricular dilatation. In these cases raised ICP was thought to be a contributory factor, although ICP was not measured. Horikawa (1991) reported a rapid fall in blood flow

velocities and pulsatility following shunt implantation, whilst ventricular size was only slightly reduced, suggesting that changes in pulsatility were mainly affected by ICP.

According to two studies (Alvisi *et al.*, 1985; Van Bel *et al.*, 1988), decreased cerebrovascular compliance due to raised ICP caused an increase in SPFV with a subsequent increase of RI in hydrocephalic children. However, ICP was not measured in either of these studies. More recent studies (Deeg *et al.*, 1988; Huang and Chio, 1991; Goh *et al.*, 1991a, 1991b) have shown that increased pulsatility follows a marked increase in EDFV, because the significant fall in pulsatility following CSF drainage is due to a significant increase in EDFV. This suggests that the RI may be a reliable reflection of the distal cerebrovascular resistance. The use of Doppler indices in clinical management has also been investigated. Chaddock *et al.* (1989) reported a mean RI of 0.84 in 46 neonates with symptomatic or progressive ventriculomegaly, which decreased to 0.72 after shunting. Goh *et al.* (1991a), Horikawa (1991) and Nishimaki *et al.* (1991) have found similar RI values, suggesting RI values > 0.8 as the criterion for shunting or assessing shunt function in young infants. Generally, RI values persistently above 0.8 in neonates and 0.65 in infants suggest that ICP may be elevated. Norelle *et al.* (1989) reported mean PI values of 1.06 in stable ventriculomegaly, 1.72 in progressive hydrocephalus prior to shunt placement, and 1.02 after shunting.

Some authors suggest that, because there is a wide range of reference values and an overlap between normal and abnormal values, the usefulness of PI and RI measurements lies in their employment on an individual basis, particularly in terms of patient follow-up (Chaddock and Seibert, 1989; Seibert *et al.*, 1989). Raised pulsatility (both PI and RI) has been claimed to be a reliable indicator of shunt dysfunction, which is associated with raised ICP (Chaddock *et al.*, 1991; Pople *et al.*, 1991). A significantly decreased RI following shunt revision was also found (Chaddock *et al.*, 1991). Another study (Pople *et al.*, 1991) showed that patients with confirmed shunt blockage had a PI value two standard deviations above the mean for asymptomatic shunted children of their age.

Although most studies found an increased pulsatility in patients with progressive hydrocephalus, two studies (Grant *et al.*, 1987; Anderson and Mawk, 1988) concluded that the pulsatility indices did not contribute significant diagnostic clues in hydrocephalus. Grant *et al.* (1987) found no significantly raised RI values in 10 patients with progressive hydrocephalus. Anderson and Mawk (1988) reported increased pulsatility in only one-third of their hydrocephalic patients requiring shunting. It is conceivable however, that as ICP was not measured in either study, some of their patients may have been in a stable condition without raised ICP.

In addition to the static measurements in the studies mentioned above, a few dynamic Doppler investigations of the relationship between flow velocity changes and alterations in ICP have been performed. Studying directly the hydrodynamic changes could prove to be clinically more useful, as the major concern in cases of raised ICP is the risk of secondary ischaemic insult to the brain tissue. Volume manipulation, carried out by Drayton and Skidmore (1986) during therapeutic CSF drainage, showed an exponential decline of PI. The pattern of decline of the RI was similarly studied by Minns *et al.* (1991), who defined a 'volume bloodflow response' (VFR), a possible index of volume buffering reserve. Goh *et al.*

(1992a) also studied spontaneous episodic ICP changes during REM sleep, in relation to flow velocity measurements, in hydrocephalic children and discussed the possibility of flow velocity as a reflection of cerebral haemodynamic compensation.

Previous Doppler studies in infantile hydrocephalus have reported conflicting conclusions on the significance of PI and RI, in regard to intracranial haemodynamics. Both PI and RI are significantly influenced by extracranial factors and have a wide range of reference values (Bode and Wais, 1988; Deeg *et al.*, 1988; Brouwers *et al.*, 1990; Chadduck *et al.*, 1991; Pople, 1992). Furthermore, the relationship between Doppler indices and ICP has been founded mostly on assumptions derived from clinical symptoms; only a few Doppler investigations have been related directly to adequately measured, actual ICP values. Above all, most of the measurements were carried out over a very short period of time, covering a very limited number of cardiac cycles. The complexity of intracranial CSF hydrodynamic responses however, requires long-term monitoring in order to obtain reliable data (Evans, 1992).

The aim of the present study was to assess the relationship between mean values of transcranial Doppler indices and ICP in pre- and postoperative long-term measurements, against the background of the earlier findings in infantile hydrocephalus as described in the literature (for a summary, see *Table 1*). In addition, to evaluate the reliability of TCD variables in predicting raised ICP, the relationship between these variables and ICP at any particular moment, was investigated by analyzing the effect of incidental ICP fluctuations on the TCD variables, in long-term simultaneous ICP/TCD measurements.

Materials and Methods

Materials

The relationship between ICP and TCD variables was investigated by analyzing two groups of simultaneous recordings. Group I consisted of pre- and postoperative measurements showing a significant drop in ICP (5 mmHg or more) after shunt implantation for progressive hydrocephalus. Group II consisted of TCD measurements during significant ICP changes (5 mmHg or more). The patients in whom the group II recordings were made, were diagnosed as having either clinically progressive hydrocephalus (primary or as a result of shunt dysfunction) or clinically stable hydrocephalus. All hematocrit values were within the normal ranges for age. The hydrocephalus aetiologies included: aqueductal stenosis and spina bifida; posthemorrhagic hydrocephalus, postmeningitic hydrocephalus, and idiopathic communicating hydrocephalus were also represented.

Data-acquisition

All of the continuous simultaneous ICP/TCD measurements were carried out over a minimum period of one hour, using a 2 MHz pulsed Doppler instrument (TC 2-64B EME, Ueberlingen, Germany). The transducer was equipped with acoustic focusing and had a diameter of 22 mm. The middle cerebral artery on the side contralateral to the ventriculoperitoneal shunt (VPS), was chosen for its accessibility and reliability and was insonated through the temporal bone using the technique described by Aaslid *et al.* (1982). The total emitted energy was 50 - 100 mW/cm², which is within the safety limits of cranial ultrasonography. The focal depth varied in 5 mm increments and was set at the point which obtained the highest Doppler signal when moving slightly away from the bifurcation. With a burst width of 13 μ s, the sample volume had an axial extension of approximately 10 mm. The TCD system performed a real-time spectral analysis on the ultrasound signal. A spectrogram display with time increments of 3 seconds recording time was used. The system calculated a mean flow velocity (MFV) and a Pulsatility Index (PI = (S - D)/M; peak systole (S), end-diastole (D), mean (M)), which was shown on the screen. The MFV velocity was defined as the time-mean value of the Doppler velocity spectrum envelope. After every ten consecutive stable waveforms, a print was made on a high-resolution printer for interpretation. Systolic peak flow velocity (SPFV) and end-diastolic flow velocity (EDFV) for each printout was measured manually. The Resistance Index (RI) was then calculated (RI = (S - D)/S)). Hematocrit values were obtained before every measurement. The heart rate was within physiological limits during each measurement. The risk of disturbing the state of the infant made reliable CO₂ measurements impossible.

Non-invasive ICP measurements were carried out simultaneously, using a fontanometer. The Rotterdam Teletransducer (RTT), a telemetric device based on the applanation principle, is a reliable instrument for measuring ICP through the anterior fontanelle (De Jong *et al.*, 1984b; Overweg-Plandsoen, 1990). The advantage of this device in comparison to others, is that the RTT can be easily calibrated before and after every measurement. In an earlier study, the present authors examined different aspects of the RTT and validated the fontanelle pressure measurements with simultaneous intraventricular pressure measurements. It is accepted that fontanelle pressure measurements, like the epidural method, produce slightly higher ICP values than intraventricular measurements. The anterior fontanelle pressure (AFP) data, along with heart rate and respiration data, were acquired using a specially designed multiple channel registration program and stored into a computer for further calculations. Mean arterial blood pressure was calculated using a DYNAMAP[®] automatic blood pressure measuring device, specially equipped for small infants. Each time a TCD printout was made during the simultaneous fontanelle and TCD measurements, this was marked on the AFP recording paper as well as in the computer. The children slept naturally (no sedatives were used) during most of the measurements (state of the infant: stadium 1, according to Beintema and Prechtl criteria (1968)).

Statistical analysis

Paired *t*-tests were used to compare pre- and postoperative means (Group I). In order to analyze associations between variables, such as differences between pre- and postoperative values, and between AFP and Doppler variables, Pearson's correlation coefficients were computed and tested for significance using a student's *t*-table (Group I). Correlations were computed for each simultaneous AFP/TCD measurement (Group II) and average correlation coefficients with 95% confidence intervals were calculated using bootstrap methods (Efron and Tibshirani, 1993).

In addition, each simultaneous AFP/TCD measurement was divided into parts made up of 20 - 30 cardiac cycles. The mean and standard deviation of the AFP and Doppler indices were calculated. In this way short-term measurements were created to demonstrate variation in PI and RI in the course of a whole measurement.

Table 1. Intracranial Doppler investigations in childhood hydrocephalus.

Reference	Size and Age of population	FD or TCD	Insonated vessel	PI	RI	ICP AFP
Hill and Volpe 1982	N=11 13-180 days	FD	ACA	-	↑	(Ladd) AFP ↑ or normal
Alvisi 1985	N=10 < 1 year	FD	ACA	↑	-	-
van Bel 1988	N=10 GA: 26-32 weeks	FD Duplex	ACA	↑ ↓ after VPS	-	-
Deeg 1988	N=17 GA: 41 ± 6.5 weeks	FD Duplex	ACA	↑	-	AFP ↑
Anderson 1988	N=29 < 1 year	FD Duplex	ACA/MCA	↑	-	-
Chaddock 1989	N=46 < 1 year	FD Duplex	ICA/ACA/MCA	-	↑	-
Fischer 1989	N=9 < 1 year	TCD	ICA/ACA/MCA	↑	-	-
Norelle 1989	N=24 7 days-14 years	TCD	MCA	↑	-	-
Quinn 1989	N=35 GA: 38 weeks-4.5 years	TCD	MCA	↑	-	-
Chaddock 1991	N=52 11 months-17 years	TCD	ICA/ACA/MCA	-	↑	ICP ↑
Goh 1991	N=14 1 day-12 years	TCD	MCA	-	↓ after VPS	ICP ↓
Minns 1991	N=11 35 weeks-10 years	TCD	MCA	-	↓ after CSF ↓	ICP ↓
Huang 1991	N=14 7 days-8 months	FD Duplex	ACA	↑	-	-
Pople 1991	N=63 mean: 74 months	TCD	MCA	↑ shunt dysf.	-	ICP ↑ (shunt reservoir)
Sanker 1991	N=41 < 16 years	TCD	ICA/ACA/MCA	↑	-	ICP ↑
Goh 1992	N=18 4-11 months	TCD	ACA/MCA	-	↑ ↓ after CSF ↓	ICP ↑
Goh 1992	N=7 1-10 years	TCD	MCA	-	↑ or ↓	ICP ↑

FD: fontanelle Doppler; TCD: transcranial Doppler; PI: Pulsatility Index; RI: Resistance Index; ACA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery; ICP: intracranial pressure; AFP: anterior fontanelle pressure; VPS: ventriculo-peritoneal shunt; GA: gestational age.

Results

Group I covered 3180 pre-operative and 3140 postoperative cardiac cycles in 15 paired measurements, with group II covering a total of 6600 cardiac cycles in 22 measurements.

Group I: fifteen corresponding pairs of adequate PI or RI and AFP data were available in 15 patients. In all of the pre-operative measurements AFP was abnormal (patient age < 1 month: 9 ± 2 mmHg; patient age > 1 month: 11 ± 2 mmHg) (Overweg-Plandsoen, 1990), returning to normal in 11 of the patients after successful CSF drainage. Of the 4 measurements (nos. 1,8,9,14), which remained abnormal, AFP was only slightly elevated (*Appendix 1*). The postoperative decrease in mean AFP varied from 26% to 73% (mean: 49.4%). Of the pre-operative PI values, six were abnormal (nos. 3,5,7,10,11,12), by the standard of their age-related reference values (Brouwers *et al.*, 1990; Pople, 1992) and all but one (no. 5) returned to normal after CSF drainage. The mean decrease in PI was 25.3% (range: 11 - 45%). Of the pre-operative RI values, five were abnormal (nos. 5,7,10,11,12) by the standard of age-related reference values (Bode and Wais, 1988) and only 3 of them (nos. 5,10,11) returned to normal. The mean decrease in RI was 13.2% (range: 1 - 24%). In one measurement (no. 4) there was a slight increase in both PI and RI following CSF drainage,

Table 2. Correlation (r) between anterior fontanelle pressure (AFP) and transcranial Doppler (TCD) variables in pre- and postoperative measurements.

variables correlated	pre-operative		postoperative	
	r	p-value	r	p-value
AFP/PI	-0.28	NS	-0.33	NS
AFP/RI	-0.25	NS	-0.20	NS
AFP/MFV	0.34	NS	0.54	<0.05

despite a substantial AFP decrease. Paired *t*-test showed a significant mean difference ($p < 0.001$) between pre- and postoperative values for all four variables examined. As far as the association between variables was concerned, significant correlations between PI, RI and MFV values were shown. No significant correlations between the Doppler variables and AFP could be calculated (*Table 2*).

Group II: 22 continuous simultaneous AFP/TCD measurements with substantial AFP variations were analyzed (*Appendix 2, Figure 1*). The mean AFP ranged from 13.2 to 36.8 mmHg, with AFP fluctuations varying from 8 to 33 mmHg. SPFV and MFV showed significant correlations with AFP in 21 measurements and EDFV showed significant correlations in 16 measurements. Both PI and RI however, showed poor or negative correlations with AFP in the individual measurements, ranging from -0.84 to 0.49 (PI) and from -0.80 to 0.50 (RI), showing significance in only 14 measurements. SPFV and MFV

showed the best average correlations with AFP. Both PI and RI revealed poor or negative average correlations with AFP (*Table 3*).

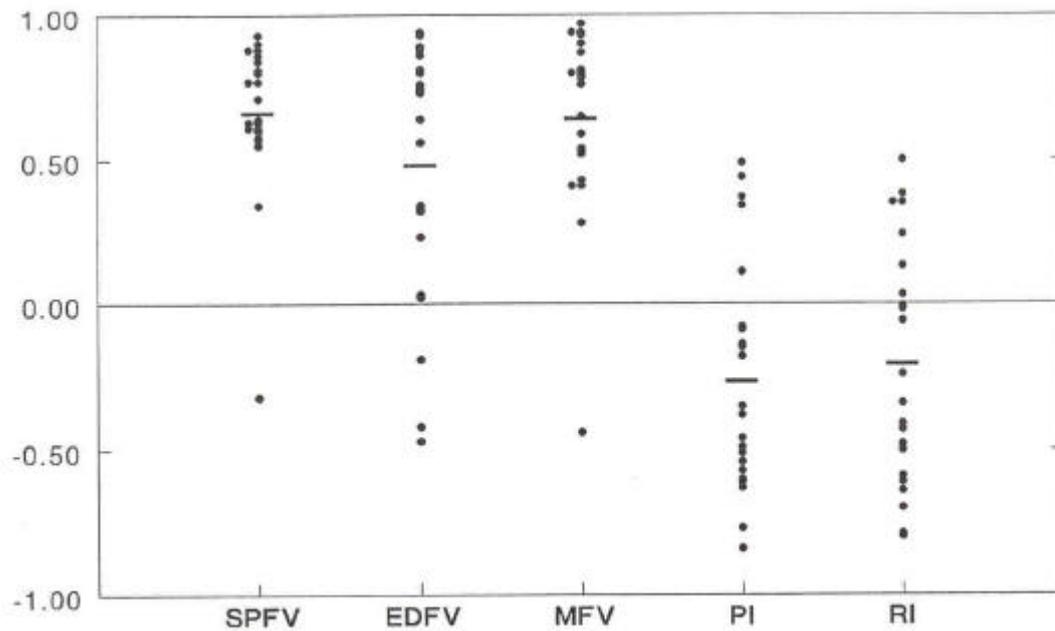


Figure 1. Pearson's correlation coefficients between AFP and SPFV, SDFV, MFV, PI and RI in children with hydrocephalus.

Table 3. Simultaneous AFP/TCD measurements: average correlation coefficients (r) between TCD variables and AFP, with 95% c.i. (bootstrap method).

TCD variable	mean correlation coefficient	standard deviation	bootstrap t -interval (95% c.i.)
SPFV	0.66	0.26	0.46 - 0.75
EDFV	0.48	0.44	0.22 - 0.65
MFV	0.65	0.32	0.44 - 0.76
PI	-0.26	0.40	-0.41 - -0.01
RI	-0.21	0.42	-0.37 - -0.01

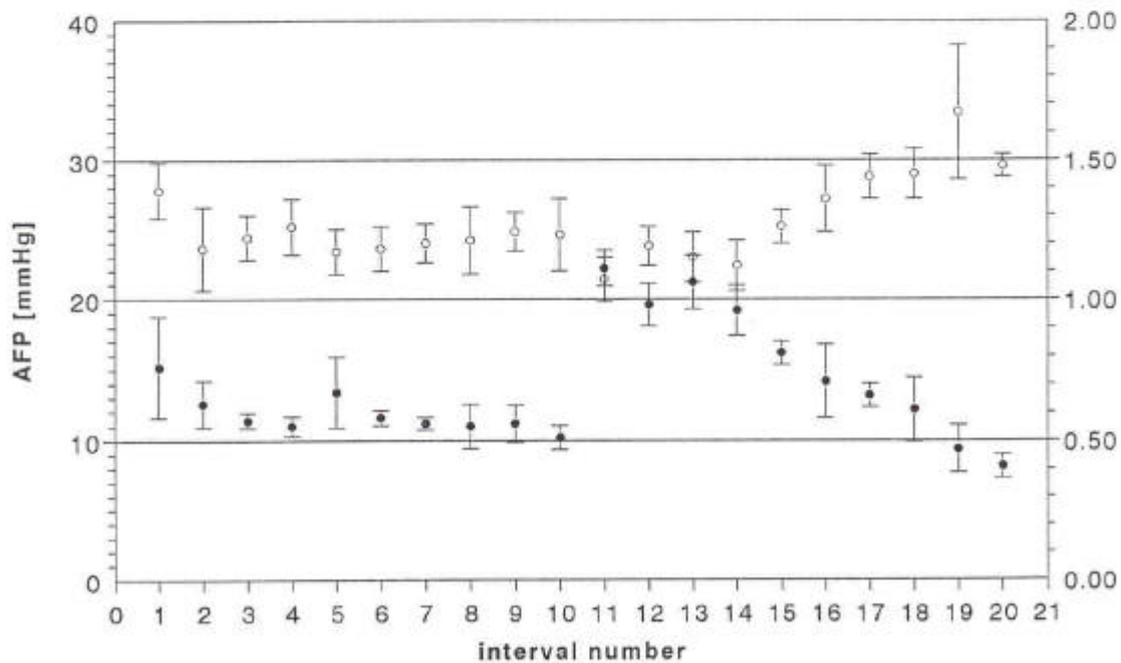


Figure 2. Simultaneous AFP/TCD measurement with a sudden increase in ICP (interval no. 11), divided into parts consisting of 20 cardiac cycles (corresponding to short-term measurements); • AFP, ○ PI.

By dividing the measurements into parts made up of 20 - 30 cardiac cycles, similar to a short-term measurement, the risk of generating a false positive or false negative relation between the Doppler indices and AFP could be clearly demonstrated (*Figure 2*). In the case presented in *Figure 2* (interval nos. 14 to 19), PI increased while AFP decreased.

Discussion

Besides monitoring ICP in progressive childhood hydrocephalus, measuring the effect of raised ICP on cerebral haemodynamics might be of importance in determining the moment for shunt implantation. An alternative non-invasive method of monitoring intracranial dynamics is desirable, especially when the anterior fontanelle is closed and only invasive ICP measurement techniques are possible. The value of transcranial Doppler (TCD) ultrasonography has been examined in this context.

Since TCD examination is non-invasive, causes negligible discomfort, and can readily be repeated at the bedside, its advantages for monitoring cerebral haemodynamics are obvious. TCD flow velocities and calculated indices cannot provide absolute measurements of the actual blood flow, because the actual individual cerebral arterial cross-sectional diameters are unknown. PI and RI measurements, could therefore result in a false interpretation of the cerebral perfusion. For the same reason, detection of spontaneous compensation in the hydrocephalic process and monitoring of shunt adequacy using TCD measurements, must be subjected to critical evaluation.

The timing of the measurements is also an important issue, because during REM sleep, for example, the cerebral blood volume increases (Sayawa and Ingvar, 1989; Goh *et al.*, 1992a) and causes a more prominent rise in ICP, with sustained plateau waves in hydrocephalic patients (Rosner and Becker, 1984), when increased intracranial volume is inadequately buffered.

Progressive hydrocephalus accompanied by elevated ICP leads to macro- and microvascular distortion, causing compression and reduction in vessel calibre with impaired cerebral perfusion (Levin *et al.*, 1984), hypoxic ischaemia, and eventual tissue destruction (Wozniak *et al.*, 1975).

Several studies have reported on raised PI and RI values in hydrocephalus, caused either by ventricular dilatation or, more often, as a direct result of increased ICP. ICP however, was not measured in most of the studies.

Seibert *et al.* (1989) have shown a significant correlation between CPP and RI in an experimental canine model. Goh *et al.* (1992b) showed a possible positive correlation between increased direct ICP measurements and RI's in the anterior and middle cerebral arteries. They did not suggest however, that the RI might be seen as an alternative measure of ICP or CPP. Nevertheless, the results of their study might support the view that RI could be used as an index of cerebrovascular resistance in patients with hydrocephalus, providing a non-invasive means of assessing the complex interaction of CSF hydrodynamics, the residual buffering capacity, and cerebral haemodynamic reserve.

CPP changes as a result of a change in ICP, with the autoregulatory response occurring mainly through an alteration of the calibre of the more distal cerebral vasculature (Kato and Auer, 1989). When no evidence of cerebrovascular disease is present, it is assumed that there is no significant change in the diameter of the middle cerebral artery (generally less than 5% (Heistad *et al.*, 1978; Kontos *et al.*, 1978) which could affect cerebral flow velocities during ICP fluctuations. Tranquart *et al.* (1994) postulated that a decrease in diastolic flow velocity with an increase in cerebral vascular resistance was significant when CPP reached a critical level, i.e., when ICP was equal to half the diastolic arterial pressure.

Goh *et al.* (1992a) differentiate between a type I response, with a decrease in MFV to raised ICP, and a type II response, with an increase in MFV despite a rise in ICP. The latter suggests an appropriate cerebrovascular response to increased ICP, with increased cerebral blood flow to maintain adequate perfusion, thereby containing little risk of ischaemic insult. They did find however, that the Doppler indices responses tend to be variable, probably because the change in cerebral arterial Doppler waveform depends on a combination of several intra- and extracranial factors.

Due to the conflicting conclusions on the value of PI and RI measurements in infantile hydrocephalus, the present study was conducted to assess the relation between ICP and TCD measurements, in an attempt to develop a non-invasive method for monitoring the effect of ICP on intracranial haemodynamics.

Our own results of simultaneous ICP/TCD measurements show an average decrease of Doppler index values with a decrease of ICP following successful shunt implantation. This, however, could not be demonstrated in all cases and sometimes the decrease was only subtle. The reason that these findings are not in agreement with those presented elsewhere is probably due to the fact that in almost all of the studies, short-term Doppler recordings (covering 5 up to 20 cardiac cycles) were analyzed. Since episodic changes in ICP occur, Doppler indices are likely to show the same pattern. For this reason we selected simultaneous long-term ICP and TCD measurements, with significant variations in ICP (plateau waves, B-waves), to assess the relationship between ICP and Doppler indices. Although the results show a drop in the average values of postoperative Doppler indices, correlations between ICP and Doppler indices within a single measurement are poor and sometimes even negative. We demonstrated that when these long-term measurements are divided up into parts (similar to short-term measurements) they may result in false negative or false positive index values.

Conclusion. From these findings, the fact that there is a wide range of reference values for the Doppler indices and the extracranial influences on these indices (heart rate), it can be concluded that the current Doppler indices are inadequate for monitoring complex intracranial dynamic responses, in patients with raised ICP.

Only with a more specific analysis of the Doppler waveform for monitoring intracranial dynamics, could interpretation of variations in serial TCD measurements provide a non-invasive measure of cerebral perfusion changes, in the follow up of individual patients.

The ultimate goal of the measurements, is to optimize the timing of shunt implantation in such a way, that unnecessary surgical intervention will be avoided, in those hydrocephalic

patients who can hydrodynamically compensate sufficiently, whilst seeking to prevent secondary ischaemic insult to those at risk.

Appendix 1. Relationship between anterior fontanelle pressure (AFP) and PI,RI and MFV in pre- and postoperative measurements (VPS).

pre/post VPS measurement case no.	mean AFP (SD) (mmHg)	mean PI (SD)	mean RI (SD)	mean MFV (SD) (cm/s)	number of cardiac cycles analyzed	age (months)
1 pre-op	22.7 (2.1)	1.52 (0.16)	0.79 (0.06)	43.3 (4.3)	230	-1.0
1 postop	14.4 (1.1)	1.17 (0.14)	0.68 (0.04)	59.0 (5.7)	260	-0.5
2 pre-op	22.5 (2.5)	1.60 (0.18)	0.82 (0.08)	44.1 (5.1)	240	-1.0
2 postop	8.4 (1.6)	1.01 (0.08)	0.63 (0.04)	56.7 (4.6)	230	2.0
3 pre-op	18.4 (2.3)	1.92 (0.32)	0.84 (0.06)	27.0 (8.1)	310	-0.5
3 postop	13.0 (3.2)	1.08 (0.15)	0.64 (0.06)	57.6 (8.5)	170	1.5
4 pre-op	15.1 (2.2)	1.13 (0.09)	0.65 (0.03)	56.3 (5.0)	170	1.0
4 postop	9.5 (0.9)	1.25 (0.10)	0.68 (0.04)	44.2 (3.1)	200	1.5
5 pre-op	23.7 (2.4)	2.36 (0.40)	0.90 (0.08)	27.7 (3.3)	170	1.0
5 postop	8.2 (0.9)	1.65 (0.21)	0.76 (0.03)	43.3 (7.2)	290	2.0
6 pre-op	23.8 (2.9)	1.31 (0.15)	0.74 (0.04)	52.9 (5.1)	240	1.0
6 postop	8.2 (1.1)	1.02 (0.06)	0.62 (0.03)	57.5 (3.1)	220	2.0
7 pre-op	24.1 (2.0)	2.39 (0.38)	0.93 (0.09)	28.2 (3.1)	170	1.0
7 postop	10.3 (1.3)	1.32 (0.16)	0.72 (0.04)	53.2 (7.1)	180	3.5
8 pre-op	20.7 (3.0)	1.40 (0.14)	0.71 (0.04)	45.0 (5.5)	210	1.5
8 postop	14.0 (3.2)	1.20 (0.12)	0.70 (0.03)	61.8 (4.9)	220	2.5
9 pre-op	19.8 (2.0)	1.37 (0.12)	0.69 (0.02)	43.3 (5.8)	190	1.5
9 postop	14.6 (4.6)	1.09 (0.17)	0.66 (0.05)	72.8 (13.8)	230	3.5
10 pre-op	18.5 (2.9)	1.82 (0.23)	0.82 (0.05)	43.2 (5.3)	120	2.5
10 postop	9.8 (1.1)	1.28 (0.13)	0.70 (0.02)	52.7 (6.7)	170	3.5
11 pre-op	21.5 (3.5)	2.12 (0.31)	0.87 (0.06)	38.4 (3.9)	240	2.5
11 postop	10.6 (1.8)	1.32 (0.17)	0.70 (0.04)	52.5 (6.4)	180	3.5
12 pre-op	21.2 (3.1)	1.67 (0.18)	0.78 (0.03)	42.4 (6.1)	370	3.0
12 postop	10.1 (1.4)	1.33 (0.17)	0.73 (0.04)	53.0 (6.9)	180	3.5
13 pre-op	39.1 (8.3)	1.17 (0.11)	0.68 (0.03)	51.1 (3.8)	200	3.5
13 postop	10.5 (2.7)	0.88 (0.08)	0.58 (0.03)	77.8 (7.1)	190	4.0
14 pre-op	53.6 (7.3)	1.17 (0.15)	0.68 (0.05)	54.7 (7.2)	140	6.0
14 postop	15.3 (1.9)	0.94 (0.10)	0.60 (0.05)	65.9 (4.5)	160	8.5
15 pre-op	17.8 (5.1)	1.28 (0.12)	0.70 (0.04)	44.9 (6.8)	180	6.5
15 postop	10.8 (1.8)	0.95 (0.08)	0.59 (0.03)	47.5 (5.0)	260	7.5
mean difference	13.0 (49.4%)	0.45 (25.3%)	0.11 (13.2%)	14.2 (38.5%)		
SD	9.2	0.31 0.07	11.2			
95% c.i.	7.9-18.1	0.28-0.62	0.07-0.15	8.0-20.4		
p-value	<0.001	<0.001	<0.001	<0.001		

Appendix 2. Correlation between Doppler variables and AFP variations in simultaneous AFP/TCD measurements (Pearson's correlation coefficient).

variable	case no.										
	1	2	3	4	5	6	7	8	9	10	11
SPFV (cm/s)	0.61*	0.55*	0.57*	0.80*	0.58*	0.71*	0.64*	0.77*	-0.32	0.63*	0.90*
EDFV (cm/s)	-0.19	0.03	0.23	0.47*	0.02	0.33	0.34*	0.73*	-0.42	0.32*	0.86*
MFV (cm/s)	0.28	0.41*	0.43*	0.41*	0.53*	0.54	0.52*	0.80*	-0.44*	0.59*	0.87*
PI	0.49*	0.37*	-0.15	0.34	-0.09	-0.08	0.11	-0.14	0.44*	-0.18	-0.63*
RI	0.35*	0.35*	-0.01	0.50*	0.24	-0.02	0.13	-0.06	0.38	0.03	-0.61*
mean PI	1.52	1.92	1.31	2.39	1.92	1.08	1.08	1.23	1.82	1.67	1.09
mean RI	0.79	0.84	0.74	0.93	0.82	0.64	0.66	0.68	0.82	0.78	0.66
number of cardiac cycles	270	330	270	170	230	180	330	210	120	370	250
AFP range (mmHg)	17-26	12-22	16-30	18-27	17-29	8-21	15-29	9-17	14-24	15-29	10-24
AFP mean (mmHg)	20.7	15.9	23.8	22.1	26.0	13.4	20.5	13.2	18.5	21.2	14.7
age (months)	-1.0	-0.5	1.0	1.0	1.5	1.5	2.0	1.5	2.5	3.0	3.5

variable	case no.										
	12	13	14	15	16	17	18	19	20	21	22
SPFV (cm/s)	0.88*	0.61*	0.88*	0.34*	0.86*	0.93*	0.81*	0.84*	0.60*	0.77*	0.63*
EDFV (cm/s)	0.76*	0.75*	0.81*	0.56*	0.88*	0.93*	0.74*	0.94*	0.64*	0.89*	0.80*
MFV (cm/s)	0.90*	0.79*	0.80*	0.65*	0.94*	0.97*	0.81*	0.93*	0.76*	0.94*	0.78*
PI	-0.35*	-0.61*	-0.49*	-0.46*	-0.51*	-0.38	-0.57*	-0.60*	-0.54*	-0.77*	-0.84*
RI	-0.24	-0.64	-0.70*	-0.50*	-0.41*	-0.48*	-0.43*	-0.59*	-0.34*	-0.80*	-0.79*
mean PI	1.26	1.11	1.24	1.20	1.28	1.00	1.28	1.06	1.01	1.33	1.12
mean RI	0.67	0.67	0.69	0.66	0.71	0.63	0.70	0.62	0.61	0.69	0.64
number of cardiac cycles	290	300	130	550	570	300	180	300	460	140	350
AFP range (mmHg)	13-45	14-31	19-38	13-30	7-24	17-31	12-28	12-31	17-50	15-27	28-49
AFP mean (mmHg)	25.2	19.1	25.3	17.2	13.7	21.6	17.8	18.7	29.1	17.7	36.8
age (months)	4.0	4.0	5.5	6.0	6.0	6.0	6.5	8.0	9.5	11.0	14.0

* statistically significant correlation

CHAPTER 5

MONITORING INTRACRANIAL DYNAMICS BY TRANSCRANIAL DOPPLER A NEW DOPPLER INDEX: TRANS SYSTOLIC TIME

Abstract

Since the introduction of transcranial Doppler sonography (TCD) several investigators have described the relationship between raised intracranial pressure (ICP) and Doppler waveform. This waveform has been expressed by several indices, such as the Pulsatility Index (PI) and the Resistance Index (RI). These indices are used to demonstrate the presence of raised ICP. In childhood hydrocephalus this information can be used to indicate the need for shunt implantation. However, PI and RI do prove to have certain disadvantages as both are strongly influenced by the heart rate. Moreover, both indices have a broad range of reference values, especially in children. They are therefore not very reliable for detecting insidious changes in the ICP. These drawbacks are due to the fact that these indices are composed of blood flow velocity measurements and do not embody the slope of the TCD waveform itself.

An ideal TCD waveform analysis should be performed concerning the time- related changes of the velocities. We present a hydrodynamic model, with its electrical analogue, which shows the effects of raised ICP on the intracranial haemodynamic system. Based on these physical findings we define a new Doppler index, the Trans Systolic Time, reflecting specific changes in the TCD waveform induced by changes in the mean ICP.

The applicability of this index, compared with PI and RI, is illustrated by consecutive simultaneous TCD and AFP measurements in three children with hydrocephalus.

Introduction

Accurate non-invasive monitoring of intracranial dynamics is desirable in many circumstances, for example in hydrocephalus, when direct measurement of the intracranial pressure (ICP) is not feasible or bears too great a risk. For this purpose, several authors have described the use of transcranial Doppler (TCD) blood flow velocity measurements in the basal cerebral arteries in childhood hydrocephalus (Deeg *et al.*, 1988; Chaddock *et al.*, 1989; Fischer and Livingston, 1989; Norelle *et al.*, 1989; Quinn, 1989; Goh *et al.*, 1991a; Minns *et al.*, 1991; Sanker *et al.*, 1991; Pople, 1992). Since the introduction of TCD by Aaslid *et al.* (1982) the typical velocity waveform or envelope has been described as instantaneous systolic acceleration and gradual decline during the diastole (Bode and Eden, 1989). The relatively high end-diastolic flow velocity is a characteristic of the cerebral circulation and is attributed to the low peripheral resistance in the cerebral circulation (Aaslid and Newell, 1992). Under pathological conditions the TCD waveform of the basal cerebral arteries may dramatically change. When, for instance, the ICP rises and the cerebral perfusion pressure drops, a decline in end-diastolic flow velocity can be seen (Hassler *et al.*, 1988; Klingelhöfer *et al.*, 1988). Indices to characterize the waveform or envelope do, therefore, have potential clinical significance. Several Doppler indices have been described in an attempt to quantify the waveform (Gosling and King, 1974; Pourcelot, 1974; Taylor *et al.*, 1988; Aaslid and Newell, 1992). Two widely used indices are the Pulsatility Index (PI) and the Resistance Index (RI), introduced by Gosling and King (1974) and Pourcelot (1974), respectively:

$$PI = (V_{ps} - V_{ed})/V_m \quad \text{eq. 1a}$$

$$RI = (V_{ps} - V_{ed})/V_{ps} \quad \text{eq. 1b}$$

In these equations the subscripts "ps" and "ed" indicate the peak systole and end-diastole, respectively. V_m is the time-averaged mean flow velocity.

These ratios have certain drawbacks. They are strongly influenced by the heart rate. They have a broad range of reference values, especially in children, and their relation to ICP shows large variations (Hancock *et al.*, 1983; Grant *et al.*, 1987; Anderson and Mawk, 1988; Bode and Eden, 1989; Seibert *et al.*, 1989; Brouwers *et al.*, 1990; Goh *et al.*, 1991a; Minns *et al.*, 1991; Pople, 1992). Hence, they are not very sensitive for the screening of raised ICP and monitoring intracranial dynamics. These drawbacks basically stem from the fact that these indices are composed of the actual blood flow velocity measurements. They do not reflect the slope of the TCD envelope. The response of the intracranial arterial blood flow velocity to changes in blood pressure during the cardiac cycle, bears information about the haemodynamic properties of the intracranial vascular system (Taylor *et al.*, 1988). During the cardiac cycle the arterial blood flow velocities have a characteristic pattern, reflected in the Doppler waveform. An ideal TCD waveform analysis, should therefore be focused on the velocity changes during the cardiac cycle.

This study presents such an analysis. A new Doppler index, Trans Systolic Time (TST), is defined. Using a hydrodynamic model and its electrical analogue, the physiological basis of this index is presented. The applicability of this index was examined in hydrocephalic children, analyzing simultaneous TCD and ICP measurements, demonstrating its superiority over PI and RI.

Analytical method

The waveform of the cerebral arterial blood flow velocity is related to both the cerebral perfusion pressure (CPP) and the cerebrovascular resistance (CVR) (Aaslid and Newell, 1992). The CPP is defined as the pressure over the cerebral vascular system, i.e. the difference in pressure between arterial inflow and venous outflow. For measurement purposes, a mean value is used, approximated by the difference between mean arterial blood pressure (MABP) and ICP (Portnoy and Chopp, 1983; Gaab and Heissler, 1984; Brown, 1991). The vascular resistance is related to the diameter and, to a lesser extent, to the length of a vessel. If an incompressible fluid and laminar flow are assumed, then the resistance of a vessel segment is a fourth order function of the diameter, according to the Poiseuille-Hagen equation (Permutt and Riley, 1963; Agarwal *et al.*, 1969; White, 1988). A small reduction in vascular diameter, as a result of the compression of the cerebrovascular system by increased ICP can, therefore, induce a significant increase in vascular resistance. The variation of vascular resistance due to vascular deformation was used in this model to establish a new Doppler index, Trans Systolic Time, concerning the effect of ICP on the cerebrovascular system.

Description and evaluation of the models

A schematic physiological presentation of the vascular system was used as the basis for developing a hydrodynamic model. Through an electrical analogue of this latter model, a mathematical description of the TCD envelope, which formed the basis for the TST, was derived. To discuss the clinical implications of ICP on the cerebrovascular system, the hydrodynamic model was employed. Information obtained from both models leads to a mathematical description of the new index.

Physiological model

The simplified physiological model of the cerebral vascular system is presented in *Figure 1*. It shows an intracranial and an extracranial vascular network, placed in parallel, perfused with blood by the heart. The intracranial vascular network is embedded in incompressible fluid contained in a space with fixed walls, the cranial cavity. The blood flow velocity is measured in the basal cerebral arteries.

This model is used for further evaluation of the relevance of the CVR in relation to changes in ICP and its effect on the TCD waveform during the cardiac cycle.

The buffer capacity of the spinal CSF system for raised ICP, as well as the CSF formation and absorption during one cardiac cycle was considered negligible and therefore not incorporated into the model presented in *Figure 1* (Agarwal *et al.*, 1969; ReKate *et al.*, 1988; Aaslid *et al.*, 1991). The fact that infants with an open fontanelle have an extra buffer capacity for ICP changes, has not been implemented in the different models, to uphold the general concept of the effect of ICP on cerebral haemodynamics and to avoid further unnecessary complexity. For further evaluation of the different models, blood was assumed to be an incompressible fluid.

The CVR is controlled by neurovascular regulating mechanisms. The most important of these are cerebral autoregulation, coupling between metabolism and flow, and CO₂ dependent regulation (Lassen, 1959). In healthy brain tissue, autoregulation maintains the mean cerebral blood flow (MCBF) within certain limits, by adjusting CVR to CPP changes (Strandgaard, 1976; Gaab and Heissler, 1984; Levene *et al.*, 1987). Autoregulation changes the CVR primarily, by actively varying of the diameter of the arterioles (Gaab and Heissler, 1984). The latency time of the autoregulation is in the order of one second or more (Strandgaard and Paulson, 1984; Aaslid *et al.*, 1991). This means that, in the present study population consisting of children with hydrocephalus, the instant effect of autoregulation within one cardiac cycle can be disregarded.

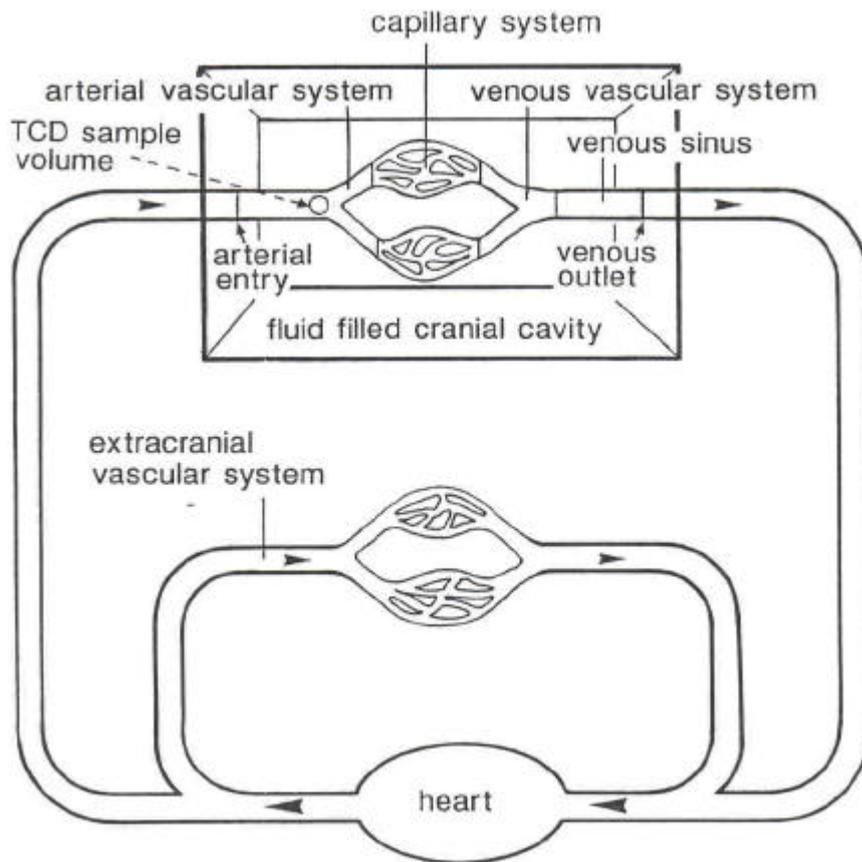


Figure 1. Physical model of the vascular system.

Hydrodynamic model

To further characterize the CVR, the physiological model was transformed into the hydrodynamic model, presented in *Figure 2*, based on studies by Agarwal (1969), consisting of an extracranial and intracranial vascular system with their capacitances and resistances.

In *Figure 2*, C_B , C_1 to C_4 represent the capacitances of vessels. The vascular resistances, distributed in reality over the different vascular compartments, are concentrated into R_B , R_1 to R_4 (Agarwal *et al.*, 1969). These capacitances and resistances are nonlinear functions of the transmural pressure (Agarwal *et al.*, 1969).

C_B is in a first order approximation constant (Hancock and Goldberg, 1983). As the walls of the capillary system can be modelled by rigid tubes (Burton, 1966; Agarwal *et al.*, 1969), and the surroundings of the venous sinus consist of rigid connective tissue, thus preventing the sinus from collapsing, C_2 and C_4 are equal to zero (Gaab and Heissler, 1984). Therefore, within these structures there is no change in volume during the cardiac cycle; R_2 and R_4 are thus considered to be constant. On the other hand, the walls of the intracranial venous vascular system and to a much lesser extent, the walls of the intracranial arterial system, are flexible.

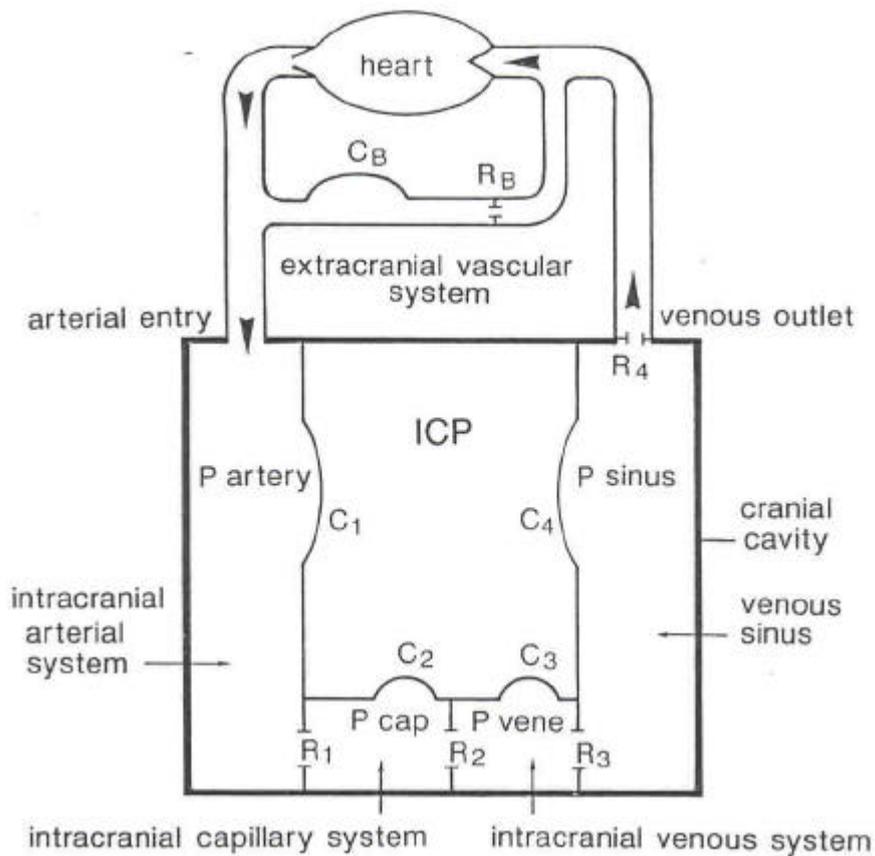


Figure 2. Hydrodynamic model. C_B : capacitance of the extracranial vascular system; C_1 : capacitance of the intracranial arterial system; C_2 : capacitance of the intracranial capillary system; C_3 : capacitance of the intracranial venous system; C_4 : capacitance of the venous sinus; P_{artery} : pressure in the intracranial arterial system; P_{cap} : pressure in the intracranial capillary system; P_{vene} : pressure in the intracranial venous system; P_{sinus} : pressure in the venous sinus; ICP : intracranial pressure; R_B : resistance of the extracranial vascular system; R_1 : resistance of the intracranial arterial system; R_2 : resistance of the intracranial capillary system; R_3 : resistance of the intracranial venous system; R_4 : resistance of the venous sinus.

Therefore, C_1 and C_3 are not equal to zero, although C_1 is small compared to C_3 , and changes in volume can occur (Agarwal *et al.*, 1969; Guyton *et al.*, 1973). Since the relative change in intracranial arterial diameter due to the cardiac output is small (Agarwal *et al.*, 1969), R_1 is considered to be constant. Variations in arterial blood volume, although negligible in their effect on R_1 , apparently have a distinct effect on R_3 , because the total intracranial volume does not change. R_3 acts like a Starling resistor. This is a collapsible tube in which the pressure external to the tube exceeds the outflow pressure (Chopp and Portnoy, 1983). As a result of the change in intracranial venous volume during the cardiac cycle, R_3 also changes, which is represented as $R_3(t)$. An increase in ICP is primarily buffered by the venous vascular system. Consequently, with increasing ICP, compression of the intracranial venous vascular

volume during the cardiac cycle, induced by variations in intracranial arterial volume, becomes relatively more apparent and $R_3(t)$ therefore increases. This relationship between $R_3(t)$ and ICP forms the basis of the TST. In infants with an open fontanelle the impact of an increase in ICP on the venous system can be less pronounced because of the extra buffer capacity of the fontanelle.

Electrical model

Fluid flow through a tube is analogous to the current through an electrical resistance (Agarwal *et al.*, 1969) To clarify further interpretation of the hydrodynamic model and to constitute the mathematical foundation for the introduction of our new Doppler index, the hydrodynamic model was transformed into its electrical analogue, as presented in *Figure 3*. Using the information, concerning the capacitances C_1 up to C_4 and the resistances R_1 up to R_4 , the intracranial system can be described as an intracranial resistance $R_C(t)$ and capacitance C_C .

In the electrical analogue of the hydrodynamic model the electrical current I , represents the substitution of the blood flow in the sample volume. This blood flow is related to the arterial blood flow velocity in the sample volume, as measured by transcranial Doppler (Markwalder *et al.*, 1984; Evans, 1992). The volume displacement arising from the elastic membranes is represented by the charge stored on electrical capacitances. The fixed volume of the cranial compartment is not represented in the electrical model. It is however, reflected in the relationships between the different variables.

The pressure P_{artery} is substituted by the voltage U_{in} . In the present model, I_{card} represents the cardiac output, which has a pulsatile characteristic.

From the electrical model, a mathematical description of the electrical current I and, consequently, of the blood flow velocity can be postulated. During the systolic upstroke, the capacitances, C_B and C_C , will be charged by the current I_{card} . During the diastolic downstroke, these capacitances will discharge through the resistances R_B and $R_C(t)$.

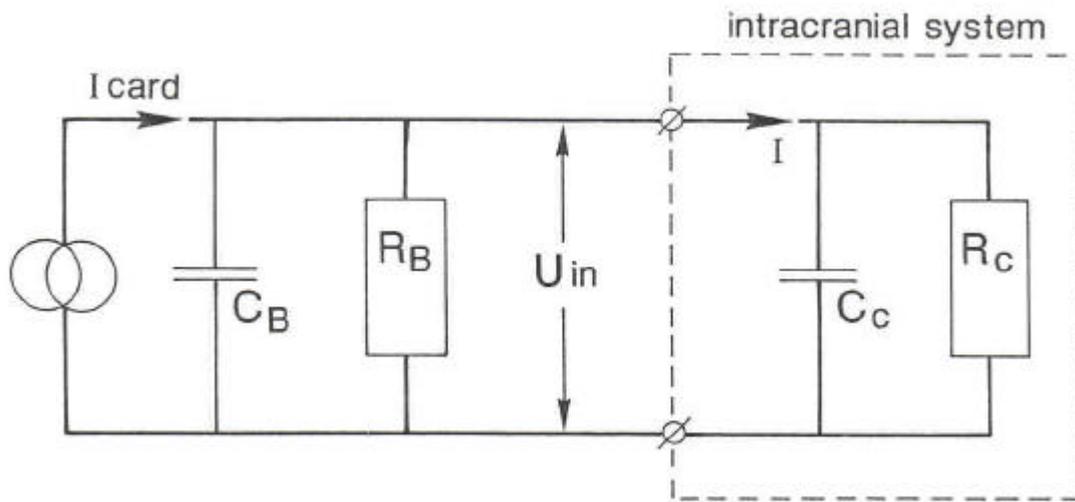


Figure 3. Electrical analogue of the hydrodynamic model. C_B : capacitance of the extracranial vascular system; C_C : capacitance of the intracranial vascular system; I : electrical input current; I_{card} : electrical current related to cardiac output; R_B : resistance of the extracranial vascular system; R_C : resistance of the intracranial vascular system; U_{in} : electrical input voltage.

Implementation of the models

The cardiac cycle can be divided into two separate periods, namely the upstroke and downstroke, as shown in *Figure 4*.

The upstroke is relatively small and practically constant, assuming no vascular pathology to be present (Milnor, 1989). During downstroke, the blood flow velocity waveform decreases towards a relatively high constant end-diastolic level.

To evaluate clinical implications of the effect of increased ICP on the arterial blood flow velocity, the hydrodynamic model (*Figure 2*) was employed. The parameters in the hydrodynamic model show a characteristic behaviour.

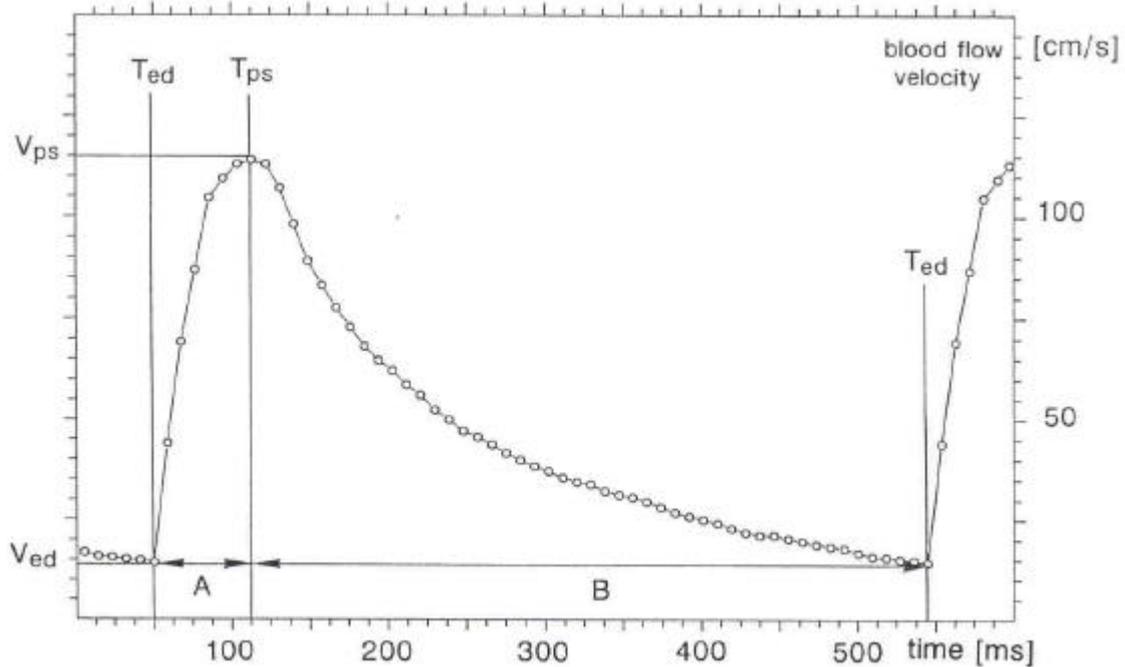


Figure 4. The TCD envelope. (A) upstroke; (B) downstroke; T_{ed} : moment of end-diastole; T_{ps} : moment of peak systole; V_{ed} : end-diastolic blood flow velocity; V_{ps} : peak systolic blood flow velocity.

The capacitance C_C , is relatively small compared to C_B (Burton, 1951; Zimmerman and Dietrich, 1987), and is considered to be constant during the cardiac cycle. During the cardiac cycle, the arterial vascular resistance R_1 can also be considered constant, although a relatively small change in diameter occurs. The corresponding impact however, of the cumulative change of the total arterial system on the venous system and therefore on $R_3(t)$ is of major importance. During upstroke, the arterial system dilates at the expense of the venous system. $R_3(t)$, which behaves like a Starling resistor (Chopp and Portnoy, 1983), will increase. During downstroke, the volume of the arterial system decreases, which enables the venous vascular volume to expand again; $R_3(t)$ decreases.

These physiological characteristics of the parameters in the hydrodynamic model (Figure 2) can be implemented into the electrical model (Figure 3) using the transformations in Appendix I. This leads to an analogue of the 'Windkessel Model' (Noordergraaf, 1978; Milnor, 1989); the electrical current I is mainly determined by C_B , R_B and $R_C(t)$.

Using the electrical model, a mathematical description of the arterial blood flow velocity during downstroke as an exponential function of time can be derived:

$$V(t) = V_{ps} \cdot \frac{R_{C(ps)}}{R_C(t)} \cdot \exp(-(T_{ps}-t)/\tau) \quad (t) \quad eq. 2a$$

or

$$V(t) = V_{ps} \cdot \frac{\tau}{\tau + (T_{ps}-t)} \cdot \exp(-(T_{ps}-t)/\tau) \quad (t) \quad eq. 2b$$

With the time constant $\tau = R \cdot C$. From the electrical model (*Figure 3*) it can be derived that:

$$\tau = \frac{R_B \cdot R_C(t)}{R_B + R_C(t)} \cdot (C_B + C_C) \quad eq. 3$$

The time-related value of $R_C(t)$ causes a characteristic relationship between blood flow velocity waveform and ICP. An increase in ICP increases $R_C(t)$, and therefore, decreases the width of the systolic peak in the blood flow velocity waveform. This phenomenon formed the basis for the development of the new time-related Doppler index, the Trans Systolic Time.

The Trans Systolic Time (TST)

From the implementation of the models, it was concluded that an alteration in ICP causes a characteristic change in the blood flow velocity waveform. A mathematical description of the shape of the curve was derived and the importance of the variations in the width of the systolic peak could be demonstrated. The new time-related Doppler index (TST), therefore, is defined as the width of the systolic peak at the level of (*Figure 5*):

$$V_{tst} = \frac{V_{ps} + V_{ed}}{\tau} \quad [ms] \quad eq. 4$$

Just as PI and RI, the TST is independent of the angle of insonation. Altering the angle of insonation changes the systolic and diastolic flow velocities equally. Thus the systolic and diastolic amplitude of the envelope, but not the shape of the curve, is affected.

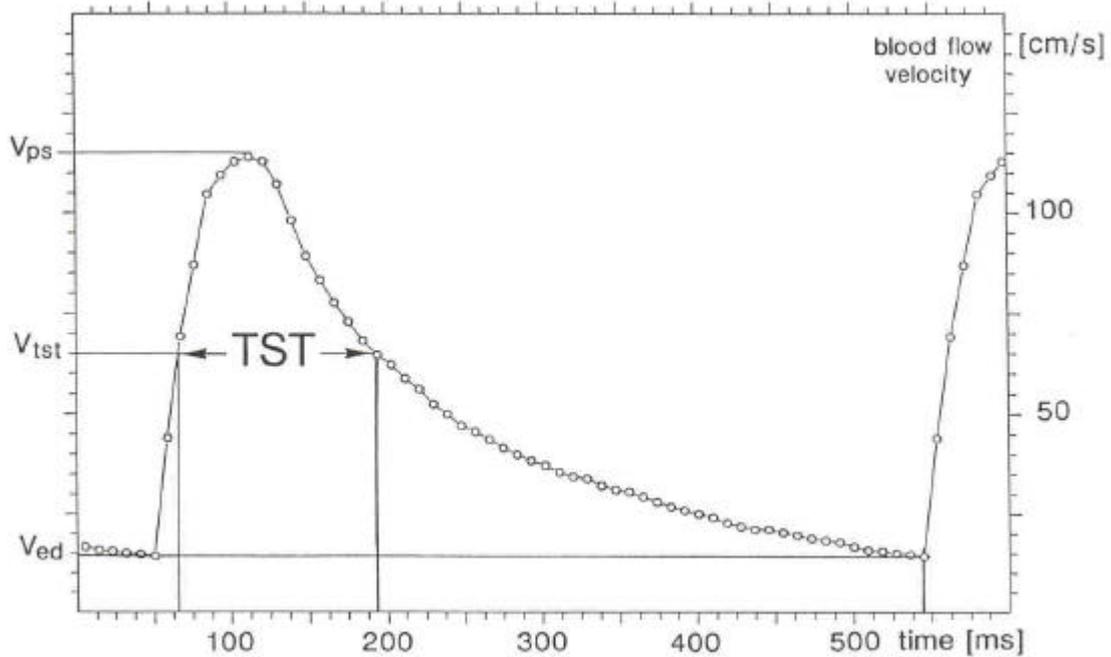


Figure 5. The Trans Systolic Time. TST: Trans Systolic Time; V_{ps} : peak systolic blood flow velocity; V_{ed} : end-diastolic blood flow velocity; V_{tst} : arterial blood flow velocity at the level $(V_{ps} + V_{ed})/2$.

Mathematically, the TST can be calculated by substitution of *equation 2 and 3* in *equation 4*. Since the upstroke can be considered constant, the width of the systolic peak is largely dependent on the shape of the downstroke. The latter is mainly determined by intracranial factors (*equation 2*).

The level of V_{tst} is solely related to the shape of the Doppler waveform and thus independent of the actual values of V_{ps} and V_{ed} .

An increase in ICP induces an increase in $R_c(t)$, and thus a decrease of the TST. This is also demonstrated by clinical data.

The decision to define V_{tst} as in *equation 4*, is based on the effect of the characteristic changes in $R_c(t)$ on the width of the systolic peak. According to *equation 3*, these changes in $R_c(t)$ lead to changes in the time constant $\tau(t)$. This time-related variation of $\tau(t)$ can be

approximated by calculating two values of $V(t)$ (V_A and V_B) during different intervals of the downstroke (separated by $t = T^*$):

$$\begin{aligned}
 V(t) &= V_A \quad T_{ps} \leq t < T^* \quad \text{eq. 5} \\
 V(t) &= V_B \quad T^* \leq t \leq T_{ed}
 \end{aligned}
 \tag{eq. 5}$$

By substituting *equation 5* into *equation 2b*, the calculated curve can be fitted on the downstroke of the pre- and postoperative measurement (*Figure 6*), by minimizing the least-square error (E) (*equation 6*).

$$E(V_A, V_B) = \sum (V(t) - V'(t, V_A, V_B))^2 \tag{eq. 6}$$

where: V = measured blood flow velocity; V' = calculated blood flow velocity and \sum = summation over the cardiac cycle.

The width of the systolic peak is largely related to the part of the downstroke described by V_A (*equation 5, Figure 6*). Therefore, the TST has to be determined in the part of the downstroke described by V_A . Furthermore, to minimize the influence of the detection error in the maximal frequency envelope, which decreases towards V_{ed} (Taylor *et al.*, 1988), the detection level of the TST is set at V_{tst} (*equation 4*), providing reliable and reproducible measurements.

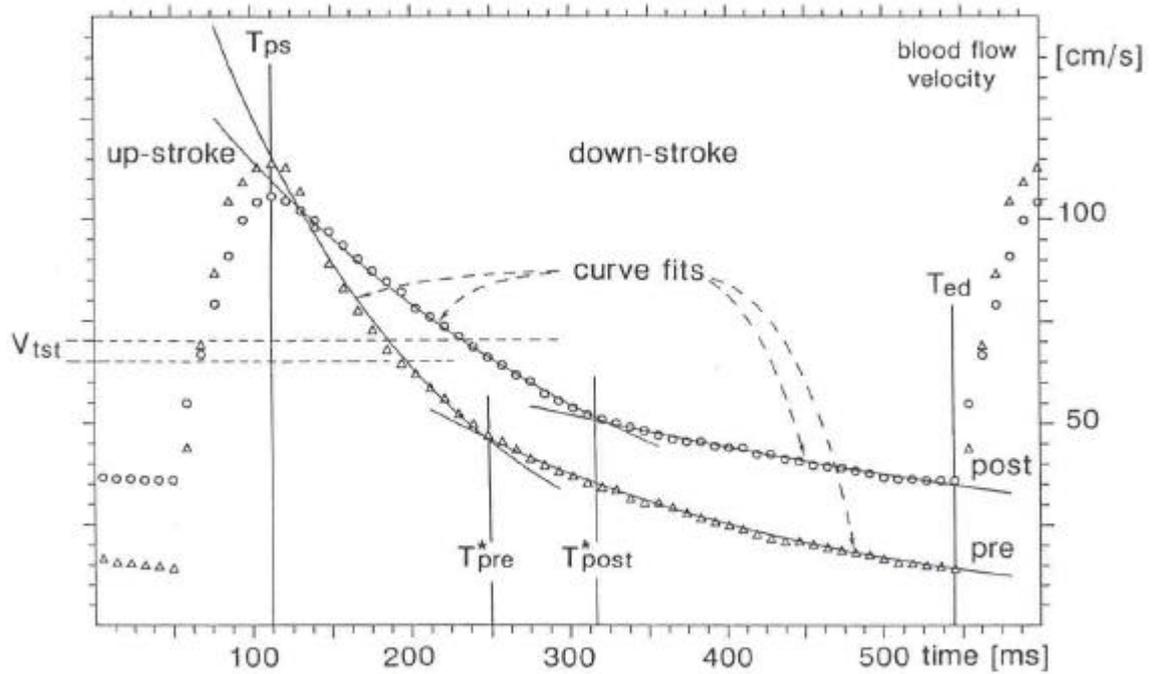


Figure 6. Pre- and postoperative TST, with curve fit analysis of the downstroke. Each downstroke is divided into two separate parts (separated by $t = T^*$), both fitted on an exponential curve. TST: Trans Systolic Time; V_{tst} : detection level of the TST; T_{ps} : moment of peak-systole.

Clinical data

Materials and methods

To investigate the applicability of the TST in clinical practice, pre- and postoperative TCD recordings in three hydrocephalic patients were analyzed. All patients were under the age of four months. They were selected for shunt implantation on the basis of clinical symptoms and underwent TCD and ICP measurements simultaneously, before and after insertion of a ventriculoperitoneal shunt (VPS). All of the continuous TCD recordings were carried out over a period of at least one hour, using a 2 MHz pulsed Doppler instrument (TC 2-64B EME, Ueberlingen, Germany). The middle cerebral artery, opposite to the side of the VPS, was chosen for its accessibility and reliability and was insonated through the temporal bone using the technique described by Aaslid (1982). The hematocrit in all patients was within physiological limits.

The TST for each single measurement was calculated, measuring the width of the systolic peak at the level of V_{tst} .

Non-invasive ICP measurements, using a fontanometer (Rotterdam Teletransducer), were carried out simultaneously. This telemetric device is a reliable method for measuring the ICP through the anterior fontanelle (De Jong *et al.*, 1984b; Plandsoen *et al.*, 1987). The TCD and ICP values, recorded simultaneously, were averaged over the measurements and the mean values of the Doppler indices and the ICP were compared pre- and postshunting.

Results

Three pre- and postoperative TCD and ICP measurements were analyzed, covering a total of 819 (245, 287 and 287) pre-operative and 804 (270, 276 and 258) postoperative cardiac cycles, respectively. After shunt implantation there was a significant decrease in ICP (respectively: 54% [mean: 24 → 11 mmHg], 48% [mean: 23 → 12 mmHg] and 67% [mean: 24 → 8 mmHg]). Postoperatively, the TST increased by 31% [mean : 152 → 199 ms], 21% [mean : 149 → 181 ms] and 22% [mean : 156 → 191 ms], respectively; PI decreased by 18% [mean : 1.35 → 1.10], 17% [mean : 1.50 → 1.25] and 18% [mean : 1.32 → 1.08]; RI decreased by 4% [mean : 0.69 → 0.66], 9% [mean : 0.76 → 0.69] and 15% [mean : 0.71 → 0.60] (*Figure 7*). Furthermore, the TST was found to be less influenced by incidental ICP fluctuations than PI and RI within a single measurement.

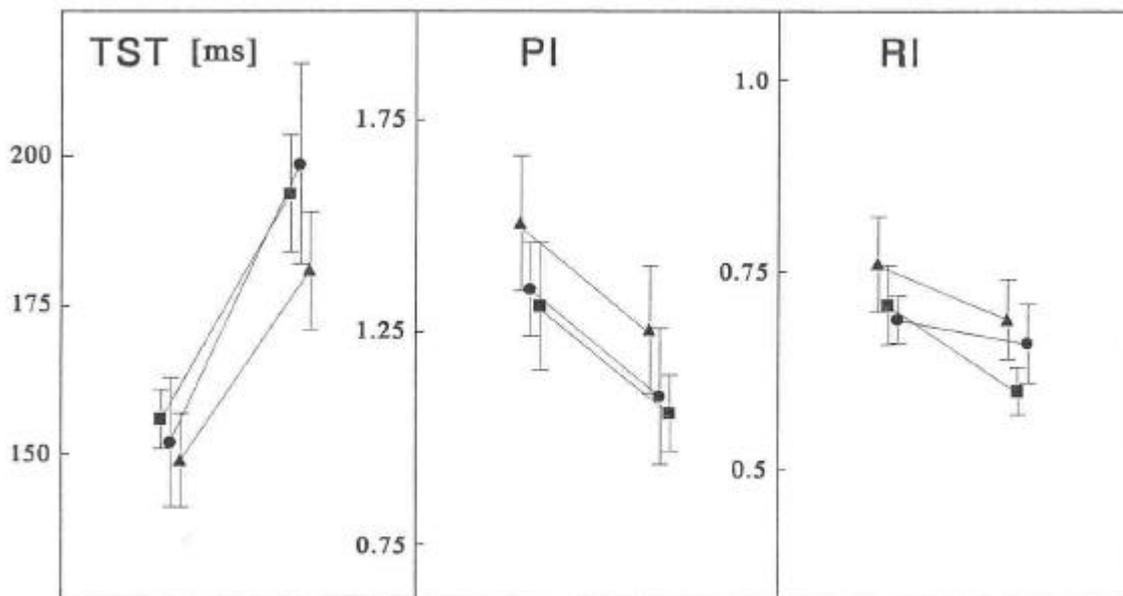


Figure 7. Comparison of the mean values (SD) of TST, PI and RI before and after shunt implantation (scales of PI and RI are relative to the scale of TST). Three pre- and postoperative measurements (, ,) in patients with hydrocephalus.

Discussion

The present study deals with the use of TCD in evaluating the effect of raised ICP on cerebral haemodynamics. TCD is non-invasive and suitable for both intermittent and continuous measurements. Several means for interpreting the Doppler signal have been described, the most commonly used being PI and RI. Because PI and RI values show large variations in relation to ICP, a new Doppler index has been developed, namely the Trans Systolic Time (TST). The TST [ms] is defined as the width of the systolic peak at the level of $V_{lst} = (V_{ps} + V_{ed})/2$. Because the TST is a time-related index, it provides a simple method of waveform analysis. The TST is based on the physical qualities, such as capacitances and resistances, incorporated in a hydrodynamic model and its electrical analogue. A mathematical description of the upstroke and downstroke of the TCD waveform is derived from these models. The upstroke is considered to be fairly constant, assuming that the integrity of the intracranial vessels is not impaired. Changes in the shape of the TCD envelope are, therefore, reflected primarily in the shape of the downstroke. Mathematically, it can be concluded, that the shape of the exponential downstroke curve is mainly determined by the cerebrovascular resistance ($R_C(t)$). Furthermore, the assumption was made that the total body resistance and capacitance, which are very much larger than their intracranial counterparts (Agarwal *et al.*, 1969; Guyton *et al.*, 1973), can be considered constant. Extracranial factors, therefore, have

less impact on the shape of the curve in the downstroke than they have on the actual values of the blood flow velocity, represented in the PI and RI ratios.

Because the TST value is strongly related to the shape of the TCD envelope, especially the downstroke, compression of the venous vascular system, induced by increased ICP, results in an increase of R_C and thus in a decrease of the TST (*equation 2b*). This is illustrated by clinical observations in hydrocephalic children. Continuous TCD recordings were performed before and after shunt implantation. TST increased significantly with a decrease in ICP after shunting.

Conclusion. According to the description of the waveform, the TST is solely related to the relative changes in the flow velocity during the cardiac cycle, primarily a function of intracranial physical properties. PI and RI however, are composed of the actual values of the flow velocities. The amplitudes of these flow velocities are the result of both intracranial and extracranial factors. Compared to PI and RI, therefore, the TST more specifically reflects the physical properties of the intracranial system.

Studying the effect of ICP on cerebral haemodynamics in hydrocephalus, could add a different point of view to the indication for shunt implantation.

Nomenclature

AFP	: anterior fontanelle pressure	[mmHg]
$C_1, C_2, C_3, C_4, C_B, C_C$: capacitance	[ml/mmHg] or [F]
CPP	: cerebral perfusion pressure	[mmHg]
CSF	: cerebrospinal fluid	
CVR	: cerebrovascular resistance	[mmHg/ml/min]
I_{card}, I	: electrical current	[A]
ICP	: intracranial pressure	[mmHg]
MABP	: mean arterial blood pressure	[mmHg]
MCBF	: mean cerebral blood flow	[ml/100g/min]
$P_{artery}, P_{cap}, P_{sinus}, P_{vene}$: blood pressure in the vascular system	[mmHg]
PI	: Pulsatility Index	
$R_1, R_2, R_3, R_4, R_B, R_C$: resistance	[mmHg/ml/min] or []
RI	: Resistance Index	
TCD	: transcranial Doppler	
TST	: Trans Systolic Time	[ms]
U_{in}	: voltage	[V]
$V, V', V_{ps}, V_{ed}, V_m, V_{tst}$: blood flow velocity	[cm/s]
, A, B	: time constant	[ms]
T_{ps}, T_{ed}, T^*	: Time indication	[ms]

Appendix 1. Equivalent variables in the two models.

Variable	Hydraulic	Electric
Effort	Pressure [mmHg]	Voltage [V]
Flow	Volume flow [cm ³ /s]	Current [A]
Capacitance	C [ml/mmHg]	C [F]
Resistance	R [mmHg/ml/min]	R []

CHAPTER 6

THE EFFECT OF INTRACRANIAL PRESSURE ON MYELINATION AND THE RELATIONSHIP WITH NEURODEVELOPMENT IN INFANTILE HYDROCEPHALUS

Abstract

The process of myelin deposition can be affected by several intracranial disorders, including infantile hydrocephalus. It is probable, that the level and duration of raised intracranial pressure (ICP) are important with respect to the extent of the parenchymal damage and delay of brain maturation.

Nineteen hydrocephalic infants were followed-up by MRI, neurodevelopmental testing (NDT) and AFP measurement. In 16 patients, with confirmed progressive hydrocephalus, shunt implantation was performed. In three patients with mild or non-progressive hydrocephalus, the decision regarding surgical intervention was postponed.

CSF volume decreased gradually after shunt implantation. The average drop in mean AFP level, postoperatively, was 55%. Postoperatively, both the degree of myelination and NDT score increased equally and substantially. There was a high correlation ($r = 0.80$) between the myelination and NDT scores. The size of the CSF volume showed a poor correlation with the mean AFP, the degree of myelination and the NDT scores. There was, on the other hand, a significant correlation between the mean AFP and the degree of myelination ($r = 0.67$) and also between the mean AFP and the NDT scores ($r = 0.70$). By means of multiple regression analysis, it was calculated that 69% of the variation in NDT, was related to the influence of mean AFP and myelination. A more long-term follow-up (mean: 27 months) showed a significant correlation between the progress of myelination and the developmental level ($r = 0.78$). Most of the children with a severely delayed myelination, pre-operatively, showed a recovery of myelination, following CSF drainage.

It can be concluded from this study that raised ICP is related to developmental outcome, through the process of myelination, but cannot account entirely, for the delay in myelination and neurodevelopment; that the delay in myelination can be (partially) reversible; and that CSF volume is of minor importance regarding neurodevelopment.

Introduction

Myelination is a dynamic process in the developing brain in infants. Magnetic resonance imaging (MRI) provides a unique means of evaluating the progress of myelination in vivo (Van der Knaap *et al.*, 1991; Fujii *et al.*, 1993; Maezawa *et al.*, 1993; Squires *et al.*, 1995). Patterns of myelination in the normal developing brain have been extensively described in MRI studies and provide reliable references to detect delayed myelination (Barkovich *et al.*, 1988; Martin *et al.*, 1988; Bird *et al.*, 1989; Van der Knaap and Valk, 1990; Grodd, 1993; Staudt *et al.*, 1993). The major part of myelin deposition occurs during the first two years of life. In the same period, swift changes occur in psychomotor development. Myelination has been claimed to be an expression of functional maturity of the brain (Flechsig, 1901, 1920). The relationship between actual myelination and neurodevelopmental testing (NDT) has been confirmed (Van der Knaap *et al.*, 1991; Fujii *et al.*, 1993; Squires *et al.*, 1995), but the prognostic value of delayed myelination for long-term outcome has not been clearly established.

The process of myelin deposition can be affected by several intracranial disorders, including infantile hydrocephalus. Hydrocephalus can lead to deteriorating intracranial dynamics, with decreased intracranial compliance and cerebral perfusion pressure (CPP) (Sato *et al.*, 1988). In this context, it has been suggested, based on transcranial Doppler investigations, that raised intracranial pressure (ICP) can cause secondary ischaemic damage to the brain (Minns *et al.*, 1991). It is likely that the vulnerable process of myelination can be adversely affected by infantile hydrocephalus. Van der Knaap *et al.* (1991) found that there is a relation between myelination and NDT, but no relation between cerebrospinal fluid (CSF) volume and NDT or between CSF volume and myelination. It is probable, therefore, that the level and duration of raised ICP are important with respect to the extent of the parenchymal damage and delay of brain maturation. Since clinical signs or symptoms of raised ICP are known to be unreliable, measuring the actual ICP, which can be done non-invasively by anterior fontanelle pressure (AFP) monitoring, can be valuable in the diagnosis and treatment of hydrocephalus in infants (Kirkpatrick *et al.*, 1989; Hanlo *et al.*, 1995). Relating the results of ICP monitoring to the progress of myelination in neonates and infants could provide important additional information in the follow-up of infantile hydrocephalus. To our knowledge no previous study has established the relationship between ICP and the progress of myelination. This study was conducted to investigate this relationship in hydrocephalic infants. For this purpose, the different correlations between myelination, neurodevelopment, ventricular dilatation and anterior fontanelle pressure were evaluated in repeated measurements.

Materials and Methods

Patients

The study, approved by the Medical Ethical Committee, included 19 patients (:14; :5) with suspected (non-tumorous) progressive hydrocephalus. The mean age on entering the study was 5.5 months (range: 1.0 - 10.0 months). Inclusion criteria were: suspicion of progressive hydrocephalus on the basis of clinical history and examination, presence of ventricular dilatation on imaging (ultrasound, computer tomography) and presence of an open fontanelle (with a diameter of at least 2 cm). Exclusion criteria were the following: (1) acute, progressive hydrocephalus requiring emergency neurosurgical intervention; (2) lesions of the brain parenchyma other than thinning of the cerebral mantle; (3) ventricular dilatation due to cerebral atrophy; (4) significant neurological deficit interfering with psychomotor development, caused by damage of the nervous system other than hydrocephalus, particularly associated with the spina bifida complex.

Methods

On entering the study, all children underwent MRI, NDT and AFP measurement. In cases of confirmed progressive hydrocephalus, shunt implantation was performed, followed by MRI, NDT and AFP measurement after six weeks and six months. All patients were also checked for shunt function three months postoperatively by clinical examination and AFP measurement. In dubious cases (mild or non-progressive hydrocephalus) the decision about surgical intervention was postponed. MRI, NDT and AFP measurements were repeated after three months. A more long-term follow-up regarding neurodevelopment was performed at a certain point during follow-up for the total study population, ensuring a follow-up period of at least 15 months.

MR imaging

MR investigations were carried out on a 1.5 Tesla Philips Gyroscan[®]. T₂-weighted spin echo images (repetition time 3000 msec, echo times 50 and 150 msec) and T₁-weighted inversion recovery (IR) images (repetition time 3000 msec, inversion time 800 msec, echo time 30 msec) were made in the transverse plane to evaluate the progress of myelination. The state of myelination in each investigation was estimated by the same observer (MSvdK), according to the criteria stated by Barkovich *et al.* (1988, 1990). The progress of myelination was assessed in months and expressed as a percentage of the age in months, in conformity with previous investigations by our group (Van der Knaap *et al.*, 1991).

The ventricle-skull ratio (VSR: maximum diameter of the frontal horns, plus the diameter of the ventricles at the level of the cella media, plus the maximum diameter of the occipital horns, over the maximum internal skull diameter) showed the highest correlation (r : 0.89) with the actual intracranial CSF volume, as calculated by MR volume measurements (Van der Knaap *et al.*, 1992). The VSR was, therefore, used to assess the size of the ventricles, as an indication of the severity of hydrocephalus on the MR images.

Neurodevelopmental testing

To avoid interobserver variations, all NDT's were carried out by the same investigator (MS). The Bayley Scales of Infant Development were used to estimate mental and motor development (Bayley, 1969). These scales are applicable between the ages of 2 and 32 months and were chosen for their reliability and validity in assessing development of infants (McCall *et al.*, 1972; Yang, 1979). The mean between the levels of mental and motor development was used as an estimation of the general psychomotor development of the child. The progress of psychomotor development was assessed in months and expressed as a percentage of age in months. To assess long-term outcome, either the Bayley Scales or the McCarthy Scales of Children's Abilities (Van der Meulen and Smrkovsky, 1986; applicable between the ages of 2.5 - 8.5 years) were used, depending on the age at follow-up.

Anterior fontanelle pressure measurement

Non-invasive ICP measurements were carried out, using the Rotterdam Teletransducer (RTT), which is a reliable technique for anterior fontanelle pressure (AFP) measurements, with a high correlation (r : 0.96 - 0.98) between AFP and intraventricular pressure (Peters *et al.*, 1995). The fontanelle diameter should be at least 2 cm to ensure adequate pressure recordings. All pressure measurements were continuous measurements, lasting up to 30 hours. Calibration of the RTT was performed before and after each measurement, to check for zero drift. Mean AFP values were calculated by computer analysis of the AFP data, using a specially developed software program (CRANIEEL[®]). A continuous non-invasive measurement technique of blood pressure in infants was not available at the time of this study. Blood pressures were evaluated on an intermittent basis. Exact calculations of the cerebral perfusion pressure, therefore, was not possible. The state of the infant was scored according to Beintema and Prechtl (1968), and only reliable measurements with a limited amount of movement artefacts were evaluated.

Statistical analysis

The following Pearson's correlation coefficients (r) were calculated, to evaluate the relationship between the different variables: (1) myelination - NDT; (2) VSR - NDT; (3) mean AFP - NDT; (4) mean AFP - myelination; (5) VSR - myelination; (6) VSR - mean AFP. Correction of the correlations between NDT and myelination, NDT and VSR, and between NDT and mean AFP for the influence of mean AFP/VSR, myelination/mean AFP, and myelination/VSR, respectively, was achieved by computing the corresponding partial correlation coefficients. Furthermore, to assess the influence of a combination of the other variables on the variation in NDT, the correlations between NDT and both myelination and VSR, myelination and mean AFP, and mean AFP and VSR were computed using multiple regression analysis. To define the prognostic value of the progress of myelination in infants, the correlation between myelination (% of normal for age) at six months postoperatively and the more long-term NDT follow-up was calculated.

Results

Fifty-four MR investigations were performed on 19 children, 16 of whom were diagnosed with progressive hydrocephalus, requiring shunt implantation. Three patients had mild or non-progressive hydrocephalus, and, therefore, no surgical intervention was required. Neurological deficits were minor or absent: sunsetting or loss of upward gaze and slight distal diplegia were the only abnormalities observed in some patients. On four occasions NDT was not performed, because the patients were too young; in one patient no long-term NDT follow-up was performed.

The mean myelination age pre-operatively was 65% (SD: 14; range: 50 - 95), at six weeks postoperatively 73% (SD: 16; range: 38 - 100), and at six months postoperatively 89% (SD: 10; range: 63 - 100). The mean NDT age pre-operatively was 72% (SD: 15; range: 50 - 95), six weeks postoperatively 79% (SD: 11; range: 50 - 93), and six months postoperatively 89% (SD: 12; range: 67 - 106). The average decrease of the VSR from pre-operatively to six weeks postoperatively was 10% (SD: 11; range: 0 - 28%; in 8 patients 5%) and from pre-operatively to six months postoperatively 22% (SD: 13; range: 5 - 49%). The average mean AFP pre-operatively was 21 mmHg (SD: 4.5; range: 16 - 29 mmHg), and at six weeks postoperatively 11 mmHg (SD: 1.7; range: 8 - 14 mmHg). In only two patients an AFP value (normal in both patients) could be obtained at six months postoperatively. In the other patients the fontanelle had closed at that time, and AFP measurement was no longer possible. The results of the study are presented in *Figures 1 and 2*, an example of the progress of myelination in shunted hydrocephalus is shown in *Figure 3*. A highly significant correlation ($r: 0.80$) was found between myelination and NDT scores (*Table 1*). Also, a significant correlation was observed between mean AFP and NDT scores ($r: 0.70$) and between mean AFP and myelination age ($r: 0.67$). A poor correlation however, was found between NDT scores and VSR ($r: -0.33$), between myelination age and VSR ($r: 0.44$) and between mean AFP and VSR ($r: 0.28$).

The partial correlation coefficients for the relationship between myelination and NDT, and mean AFP and NDT, corrected for VSR, were almost equal to the correlation coefficients, indicative of the minor influence of VSR (*Table 1*). After correction for the influence of myelination, the partial correlation coefficients of the relationship between VSR and NDT and between mean AFP and NDT were both less negative than the corresponding correlation coefficients, indicative of the significant influence of myelination.

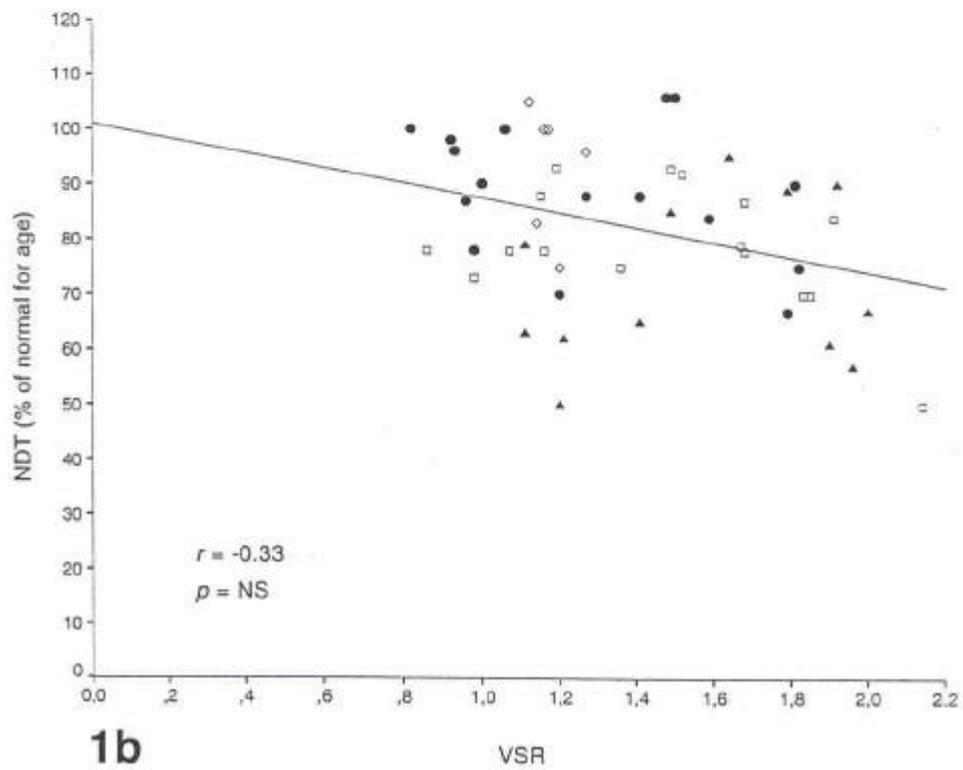
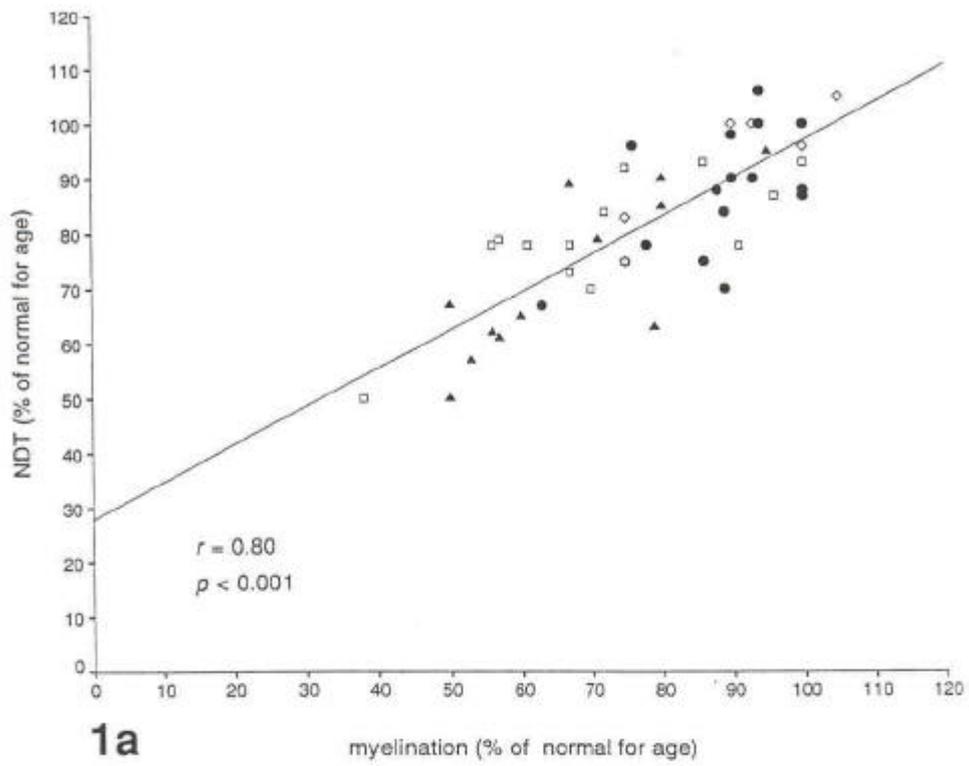


Figure 1

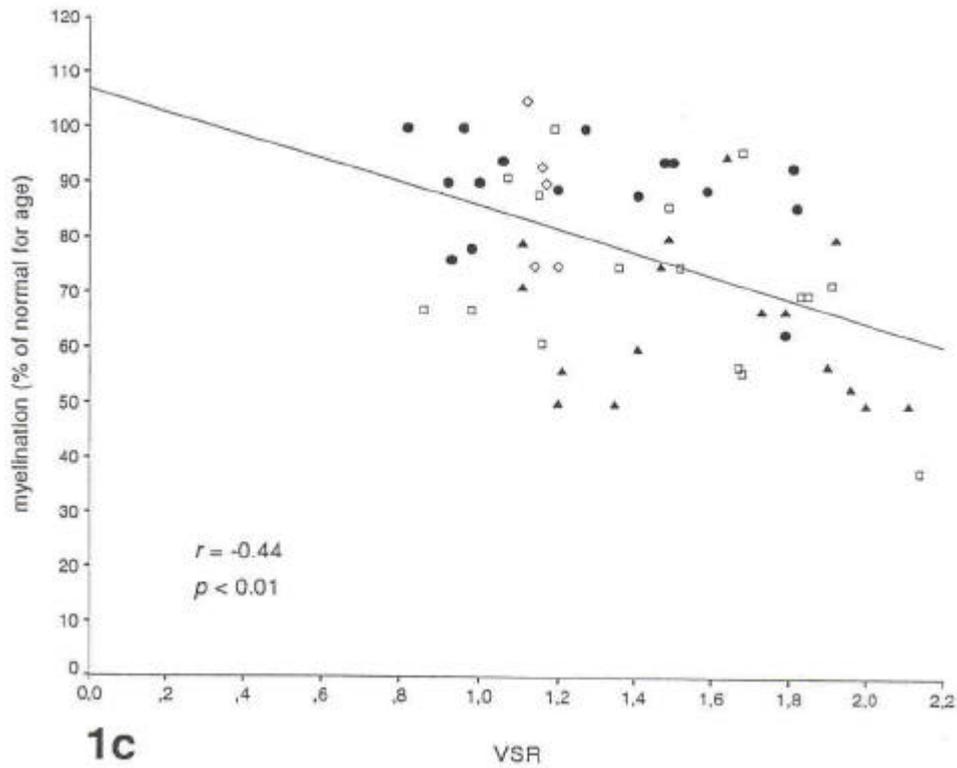
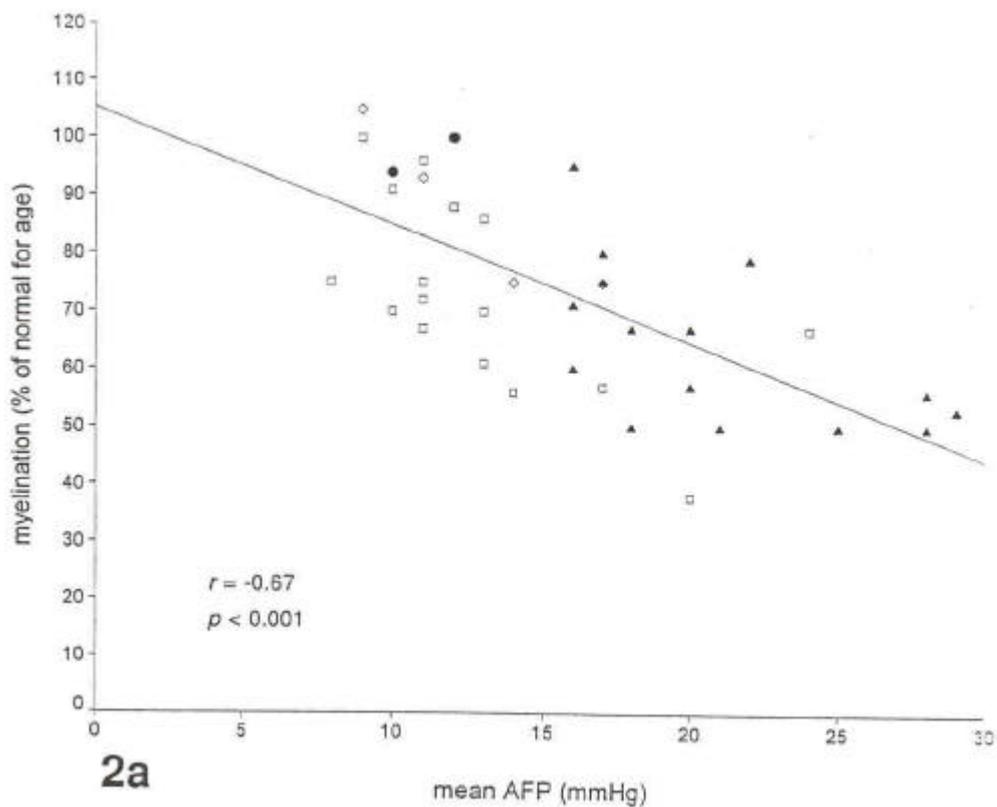


Figure 1. Relationship between (a) the progress of myelination and neurodevelopmental progress, (b) VSR and neurodevelopmental progress, (c) VSR and progress of myelination. progressive hydrocephalus before shunt implantation; ● hydrocephalus six weeks after shunt implantation; ◊ hydrocephalus six months after shunt implantation; ▲ non-progressive hydrocephalus, no shunt implantation.



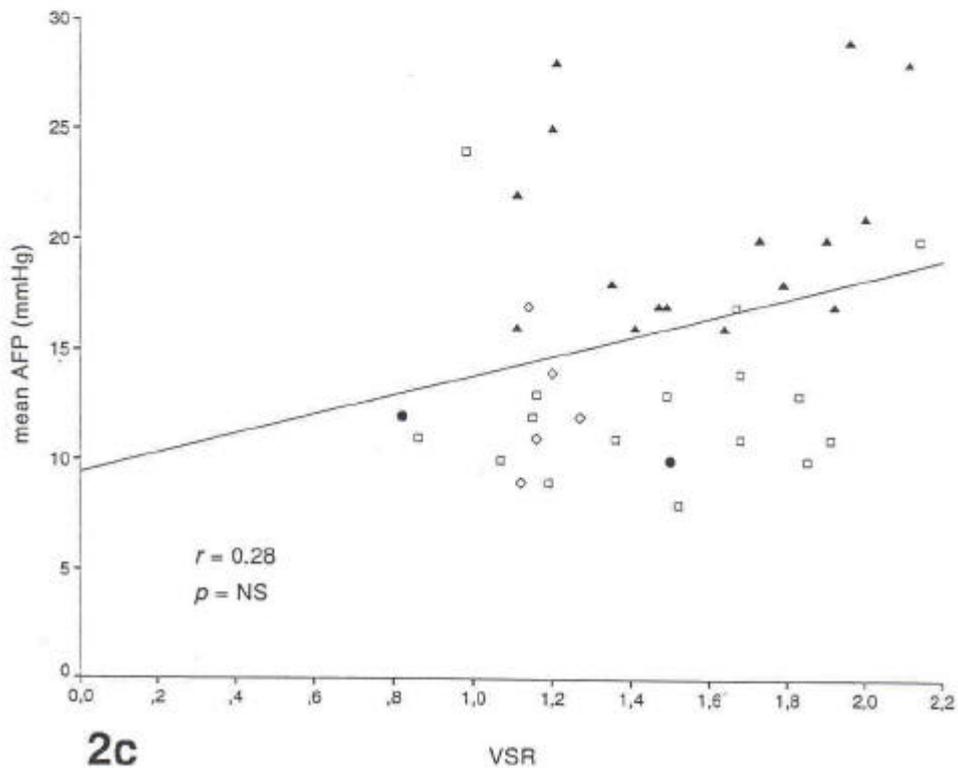
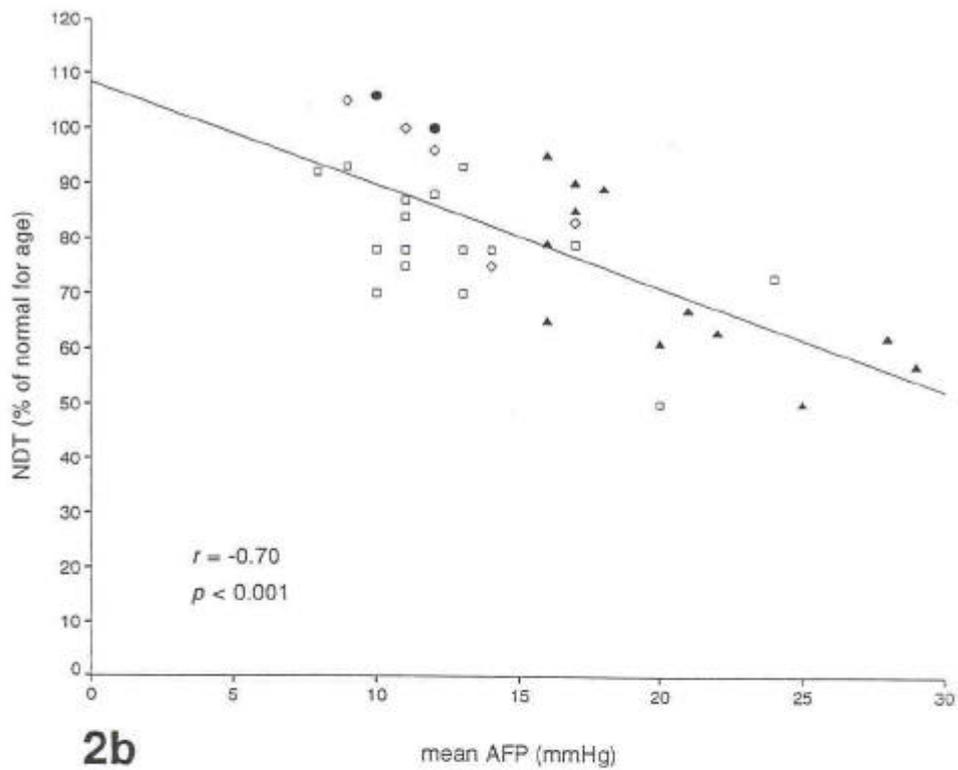


Figure 2. Relationship between (a) the mean AFP and progress of myelination, (b) mean AFP and neurodevelopmental progress, (c) VSR and mean AFP. *o* progressive hydrocephalus before shunt implantation; *y* hydrocephalus six weeks after shunt implantation; *•* hydrocephalus six months after shunt implantation; *▲* non-progressive hydrocephalus, no shunt implantation.

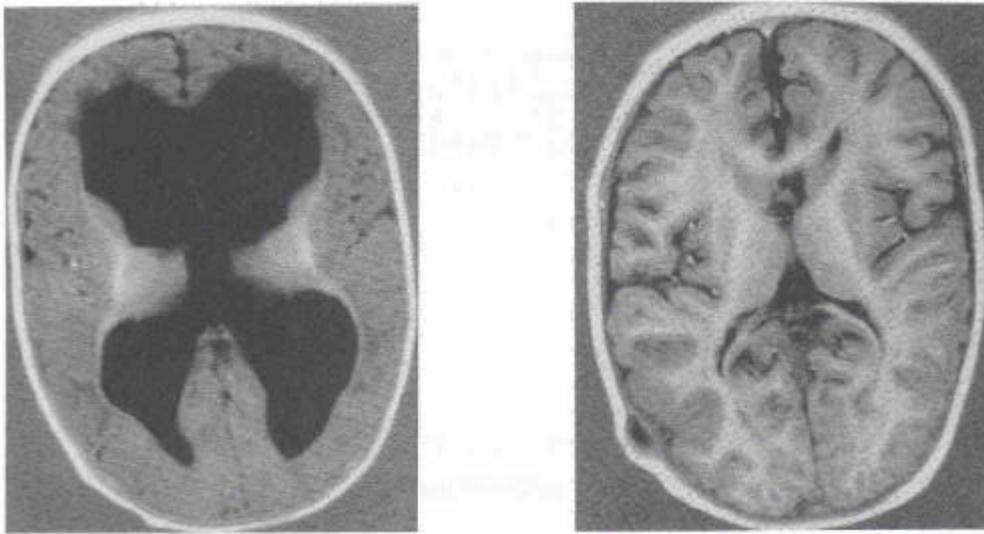


Figure 3. Progression of myelination on MRI (IR) in shunted hydrocephalus; (left) pre-operative myelination of 56% (% of normal for age); (right) 6 months postoperative myelination of 95%.

Table 1. The relationship between myelination, neurodevelopment (NDT), ventricular dilatation (VSR), and anterior fontanelle pressure (AFP).

	Pearson's correlation coefficient	Partial correlation coefficient corrected for:		
		myelination	VSR	mean AFP
myelination-NDT	0.80*		0.77*	0.63*
VSR-NDT	-0.33	0.04	-0.20	
mean AFP-NDT	-0.70*	-0.36	-0.67*	
mean AFP-myelination	-0.67*			
VSR-myelination	-0.44**			
VSR-mean AFP	0.28			

* $p < 0.001$; ** $p < 0.01$

Table 2. Correlations between a combination of variables and neurodevelopment (NDT), using multiple regression analysis.

	correlation coefficient
NDT - (myelination * VSR)	0.80*
NDT - (myelination * mean AFP)	0.83*
NDT - (mean AFP * VSR)	0.71*

* $p < 0.001$

After correction for the influence of mean AFP, the correlation between VSR and NDT was less negative and the correlation between myelination and NDT was decreased, compared to the corresponding correlation coefficients, indicative of the influence of AFP (Table 1).

Squaring the correlation coefficients (Table 1 and 2), revealed that 64% of the variation in performance on NDT was related to the influence of myelination, 49% to mean AFP, 11% to VSR, 64% to VSR and myelination and 69% of the variation in NDT was related to the influence of mean AFP and myelination. The equations defining the regression lines of the different relations were as follows: myelination - NDT: $NDT = 28 + 0.69 \times \text{myelination}$; mean AFP - NDT: $NDT = 108 - 2 \times \text{mean AFP}$; mean AFP -myelination: $\text{myelination} = 105 - 2 \times \text{mean AFP}$.

A more long-term NDT follow-up was performed in 18 patients. The mean follow-up was 27 months (SD: 10), with a mean age of 32 months (SD: 11). The correlation coefficient between the progress of myelination at 6 months postoperatively and long-term NDT follow-up was high ($r = 0.78$; $p < 0.001$) and thus, 61% of the variation in more long-term neurodevelopmental outcome was related to the progress of myelination. Five of the 8 patients with the most severely delayed pre-operative myelination (50 - 60%), showed a recovery of myelination to 85% or more at six months postoperatively (the average degree of myelination for all patients at long-term follow-up was 91%) and 7 of them showed an average to good mental function (mean: 92%) at long-term follow-up, with a distinct impaired motor function observed in six of these patients.

Discussion

Many studies have addressed the relationship between the progress of myelination and functional maturation of the brain in infants [see also the discussion in Van der Knaap *et al.* (1990, 1991)]. At first all studies concerning myelination were based on histological data (Dambaska and Laure-Kamionowska, 1990). Comparing the progress of myelination and

developmental performance in longitudinal studies was not possible at that time. After the introduction of MRI, several studies revealed the patterns of myelination in normal developing brain and patterns of delayed myelination, detected in developmentally retarded children (Martin *et al.*, 1990; Fujii *et al.*, 1993; Konishi *et al.*, 1993; Staudt *et al.*, 1993). The comparison between myelination and developmental performance however, was always qualitative. Very few studies assessed the prognostic value of the progress of myelination for final neurodevelopmental outcome (De Vries *et al.*, 1989; Guit *et al.*, 1990; Fujii *et al.*, 1993; Konishi *et al.*, 1993). Most of these studies were concerned with hypoxic-ischaemic brain damage. The correlation between myelination and psychomotor development was not calculated quantitatively. Furthermore, the severity of the parenchymal damage is hard to quantify in infants with hypoxic-ischaemic lesions. Damage to structures or processes in the brain, other than myelination, might have been responsible for psychomotor retardation. Guit *et al.* (1990) found that the progression of myelination in the early postnatal period could predict functional outcome, to a certain extent.

Van der Knaap *et al.* (1991) quantified the relationship between myelination and neurodevelopmental testing in a homogeneous patient population of hydrocephalic infants. These patients differed only in the severity of ventricular dilatation, and there was no focal parenchymal damage. Some patients had minor neurological deficits, caused only by the hydrocephalic disorder. An important advantage of this study was that the severity of hydrocephalus could be defined by calculating the intracranial CSF volume using the MR technique. A highly significant correlation between myelination and neurodevelopmental performance was found. Only poor correlations however, were found for the relation between CSF volume and both myelination and psychomotor development. Since neither the progress of myelination, nor neurodevelopmental performance was determined by the size of the intracranial CSF volume, another factor was thought to be of influence on brain maturation in these infants. The level and duration of raised ICP was considered to be potentially of importance with respect to parenchymal damage and delay of brain maturation in infantile hydrocephalus.

In a similar population of hydrocephalic infants, we performed a reassessment of the relationship between myelination, psychomotor development and ventricular dilatation (VSR) with an additional evaluation of the correlation between non-invasive ICP measurements and the variables mentioned above. We also found a highly significant correlation between myelination and psychomotor development, and a poor correlation between both these variables and the VSR. The influence of the VSR on the correlation between myelination and psychomotor development was negligible. Apparently the degree of hydrocephalus is less important than the severity of parenchymal damage and the delay of normal brain maturation, related to the raised ICP (Guidetti *et al.*, 1969).

Cerebral damage caused by progressive hydrocephalus is not entirely irreversible. We found that after decreasing ICP in infants with hydrocephalus, by shunt implantation, the progress of myelination improved, sometimes even dramatically, towards normal for age. This suggests that in these hydrocephalic infants, the delay in myelination can be, at least partially,

reversible. Similar findings concerning psychomotor development were observed, as can be expected from the correlation between myelination and psychomotor development. In most of the patients, it was not the initial pre-operative degree of myelination, but the progression of myelination after successful shunt implantation, that correlated with long-term outcome.

The present study showed a poor correlation between mean AFP and VSR. A significant negative correlation however, between mean AFP and both myelination and psychomotor development was demonstrated. From the correlation between mean AFP and myelination, we conclude that it is plausible that the process of myelin deposition is adversely influenced by raised ICP and decreased intracranial compliance in hydrocephalic infants, resulting in a delayed myelination and consequently in developmental delay.

From the data (*Table 1*) it is clear that mean AFP, as measured in this study, cannot account entirely for the delay in myelination and development found in the hydrocephalic children. An important factor, which was not evaluated in this study, regarding the extent and reversibility of the secondary ischaemic insult to the brain in hydrocephalic infants (Minns *et al.*, 1991), is probably the duration of increased ICP. Other features could be intermittent ICP changes, ICP waveform characteristics, cerebral perfusion pressure, intracranial compliance, and variation in response of the brain to these adverse factors. The pre-operative duration of raised ICP was not exactly known in the majority of our patients, because ICP was not measured repeatedly before operation and clinical symptoms related to increased ICP are not very reliable. One patient with evidence of long-standing raised ICP, showed severely delayed myelination and psychomotor development in the pre-operative period, and had no recovery during follow-up, despite adequate shunt function.

The effect of the duration of raised ICP on neurodevelopment is obviously difficult to quantify. The fact however, that psychomotor development correlated well with the progress of myelination and that ICP clearly showed a significant correlation with both the progress of myelination and psychomotor development, confirms that raised ICP is an important factor which influences the progress of myelination in infantile hydrocephalus.

Conclusion. Little is known about the relationship between raised ICP and long-term outcome in children. The results of the present study suggest however, that there is a distinct correlation between ICP and neurodevelopmental outcome in hydrocephalic infants. A decrease in ICP leads to the progress and recovery of myelination and an improvement in neurodevelopment. The treatment of patients with infantile hydrocephalus, therefore, may benefit from intensive non-invasive ICP monitoring, to prevent secondary brain parenchymal damage, which is expressed in a delayed myelination. Further research to reveal other factors that may influence the process of myelination, in particular the duration of raised ICP, is necessary. The predictive value of the early progress of myelination for truly long-term outcome (school performance, fine motor skills) has yet to be verified.

CHAPTER 7

NON-INVASIVE MEASUREMENT OF INTRACRANIAL PRESSURE IN INFANTILE HYDROCEPHALUS THE RELATIONSHIP BETWEEN RAISED INTRACRANIAL PRESSURE, SHUNT IMPLANTATION AND OUTCOME

Abstract

The role of intracranial pressure (ICP) measurements, with respect to the decision as to whether or not a ventriculoperitoneal shunt should be implanted, still remains unclear and little is known about the possible benefits of ICP monitoring, regarding long-term outcome in children. To assess the value of anterior fontanelle pressure (AFP) measurements in relation to the treatment decision, 31 hydrocephalic infants, without focal parenchymal damage on MRI, were examined. The treatment decision was taken on clinical grounds, independently from the AFP measurements. Only the mental development outcome was determined, because patients with spina bifida (inherent motor deficit) were also included in the study. All operated patients, excepting one, showed a pre-operatively increased ICP, which normalized after shunt implantation. The clinical signs in the not-operated patients, with raised ICP, were not essentially different from those in the operated group. These not-operated patients, with persistently raised ICP however, showed an average of a more than 20% reduction in mental development outcome score at the end of follow-up (average: ± 20 months), in comparison with both the not-operated patients with normal ICP and the operated patients with adequate shunt function.

Although the patient numbers in this study are rather small, we conclude, that the decision not to operate the patients with persistently abnormal ICP values, was probably incorrect. Furthermore, neurodevelopment in infantile hydrocephalus with raised ICP, even when clinical signs are less evident, can benefit from a CSF diversion procedure. Non-invasive ICP monitoring can, therefore, be a useful diagnostic procedure.

Introduction

There are still many controversies regarding the interpretation of intracranial pressure (ICP) measurements in children. Most studies on intracranial dynamics are performed in adults after neurotrauma. Some studies investigated the value of ICP monitoring in infants and children, especially in hydrocephalus (Hayden *et al.*, 1970; Di Rocco *et al.*, 1975; Vidyasagar *et al.*, 1978; McCullough, 1980; Gaab *et al.*, 1982; Colditz *et al.*, 1988; Sato *et al.*, 1988; Minns *et al.*, 1989; Anegawa *et al.*, 1991b). The potential role of ICP measurements however, with respect to the decision as to whether or not to implant a ventriculoperitoneal shunt, still remains unclear. Several other studies address the long-term outcome, with respect to neurodevelopment, in children with hydrocephalus (Di Rocco *et al.*, 1977; Dennis *et al.*, 1981; Fernell *et al.*, 1991; Pople *et al.*, 1990; Hanigan *et al.*, 1991; Kokkonen *et al.*, 1994). Little is known however, about the value of ICP monitoring to predict long-term outcome in children (Sato *et al.*, 1988; Mendelow *et al.*, 1994).

For this reason, a prospective follow-up study on the relationship between raised ICP, shunt implantation and outcome, with respect to mental development, in a consecutive series of hydrocephalic infants was conducted. A relatively new and reliable non-invasive ICP measuring technique, anterior fontanelle measurements using the Rotterdam Teletransducer, was employed (Peters *et al.*, 1995). Neurodevelopmental testing was used to assess long-term outcome in these patients.

Materials and Methods

Patients

In the period between 1991-1994, 31 infants (:16; :15) with hydrocephalus were included in the study, and admitted consecutively to the department of Child Neurology of the Utrecht University Hospital. Inclusion criteria were: (1) suspected progressive hydrocephalus based on clinical examination and ventricular dilatation on neuro-imaging (ultrasound, computer tomogra-phy, magnetic resonance imaging (MRI)); (2) anterior fontanelle diameter of at least 2 cm on entering the study. Criteria for exclusion were: (1) presence of parenchymal brain lesions, other than thinning of the cerebral mantle due to the hydrocephalic process; (2) dilatation of the cerebrospinal fluid (CSF) spaces due to cerebral atrophy; (3) significant neurological deficit likely to interfere with mental development, caused by cerebral lesions other than hydrocephalus, confirmed by MRI. The aetiology of the patients included was: aqueductal stenosis, hydrocephalus associated with spina bifida, post meningitic, idiopathic (*Table 1*).

Methods

All patients were followed-up using a standardized protocol, with regular clinical observations, neuro-imaging, developmental testing and anterior fontanelle pressure (AFP) measurements. In accordance with the protocol, patients were evaluated shortly before surgery, at one week, six weeks, three months and six months postoperatively. Those patients not operated upon, were evaluated at monthly intervals. The decision to implant a ventriculo-peritoneal shunt was made by the multi-disciplinary team of physicians involved (neurosurgeon, child neurologist and pediatrician). This decision was based only on neuro-imaging data and the most common clinical signs related to progressive hydrocephalus and raised ICP (abnormally increasing head circumference, tense fontanelle, scalp vein distension, sunsetting or loss of upward gaze, distal diplegia, vomiting, anorexia, impaired consciousness, and behaviour change). The team was not informed about the results of the AFP measurements. Whenever the team of physicians suspected progressive hydrocephalus, based on the clinical signs, shunt implantation was performed.

Anterior fontanelle pressure measurement

Non-invasive ICP measurements were carried out, using the Rotterdam Teletransducer (RTT). It has been shown that the RTT is a reliable technique for AFP measurements, with a high correlation (r : 0.96 - 0.98) between AFP and intraventricular pressure (Peters *et al.*, 1995). The fontanelle diameter should be at least 2 cm to ensure adequate pressure recordings. All AFP measurements were continuous long-term measurements, lasting up to 30 hours. Calibration of the RTT was performed before and after each measurement to check for zero drift. Mean AFP values were calculated by computer analysis of the AFP data, using a specially developed software program. Age-related AFP reference values were obtained by measuring normal infants (≤ 1 month: 9 ± 2 mmHg; >1 month: 11 ± 2 mmHg) and all AFP values above these reference values were regarded as raised or abnormal. The state of the infant during the AFP measurement was systematically scored according to the Beintema and Precht criteria (Beintema and Precht, 1968); AFP measurements with an excess number of movement artefacts (state 4 and 5) were excluded from the analysis.

Neurodevelopmental testing

To determine the outcome in each group of patients, neurodevelopmental testing (NDT) was employed by one and the same neuropsychology investigator. The Bayley Scales of Infant Development were used to estimate mental development (Bayley, 1969). These scales are applicable between the ages of 2 and 32 months. Bayley Scales were chosen for their demonstrated reliability and validity in assessing the mental development of infants (McCall *et al.*, 1972; Yang, 1979). As patients with hydrocephalus and spina bifida (inherent motor deficit) were also included in the study, only the mental development outcome was assessed and was expressed as a percentage of normal for age.

Statistical analysis

The mental development outcome scores of the different groups were compared by means of the Wilcoxon rank sum test (two-sided *p*-values). Only *p*-values below 0.05 were considered significant.

Table 1. Patient characteristics (N=31) and their relation to the initial treatment decision (shunt implantation) on entering the study.

	prevalence (%) of characteristic	% operated of patients with characteristic
Age		
≤ 1 month	42	54
>1 month	58	56
Aetiology		
aqueductal stenosis	35	73
spina bifida	29	44
postmeningitic	10	33
idiopathic	26	50
Clinical signs		
abnormally increasing head circumference	68	71
tense fontanelle	81	64
scalp vein distension	48	67
sunsetting	32	80
distal diplegia*	*41	89
impaired consciousness	10	100
vomiting	16	80
anorexia	7	50
behaviour change (including irritability)	39	75

* *spina bifida* not included

Results

The patient characteristics on entering the study and their relation to the initial treatment decision are shown in Table 1. The percentage of not-operated and operated patients were approximately equally distributed in the age categories. As far as the aetiology is concerned, patients with aqueductal stenosis were operated most often. An abnormally increasing head

circumference and a tense fontanelle appeared to be the most frequent clinical signs and approximately 70% of the patients showing these signs were operated on. Other clinical signs, like sunseting and impaired consciousness, were observed less frequently, but if present, most of the patients with these signs were operated on.

The mean follow-up of the not-operated and operated patients was 19,4 months [SD: 5.0] and 18.6 months [SD: 3.6], respectively. The relationship between AFP measurement and the initial treatment decision on entering the study is shown in *Table 2*. Eight patients with raised AFP values and dubious clinical signs of progressive hydrocephalus were not operated. The one patient with normal AFP, who was operated on nevertheless, showed clinical signs strongly suggesting progressive hydrocephalus. *Table 3* shows the relationship between normal or raised AFP on entering the study and the final treatment decision (not-operated or operated) at the end of the follow-up. During follow-up, one patient with a normal mean AFP on entering the study and no definite clinical signs of progressive hydrocephalus, was shown to have progressive hydrocephalus with raised mean AFP six weeks later and shunt implantation was performed at that time. Three patients with raised AFP on entering the study and persistent raised mean AFP values during follow-up, underwent shunt implantation at a later stage. It was ultimately decided not to operate in five patients with a normal mean AFP on entering the study and all of these patients, except one who developed a persistent mean AFP ≥ 15 mmHg, showed normal AFP values during follow-up. One of the two operated patients with normal pre-operative mean AFP, did not improve clinically and remained seriously retarded at follow-up; the clinical diagnosis of progressive hydrocephalus was probably incorrect in this case. The other patient had a normal mean AFP initially, but showed increased AFP values during follow-up. As progressive hydrocephalus, was clinically suspected, a shunt implantation was performed in this case, followed subsequently by an approximately normal mental development outcome (95%). The clinical signs of the five patients with raised AFP values (persistent mean AFP ≥ 15 mmHg) on entering the study and during follow-up and the patient who developed raised AFP during follow-up, who were not operated, did not differ consistently from those of the nineteen operated patients with raised AFP.

The median mental development score for both the not-operated group with normal AFP values during follow-up and the operated group with pre-operatively raised AFP was 100%, which is significantly different ($p < 0.05$) from the median of the not-operated group with increased AFP values (77.5%). No differences in mental development outcome, regarding aetiology were observed.

Discussion

It is often quite difficult to decide whether or not to perform shunt implantation in infants with hydrocephalus. An inappropriate decision, not to operate, can cause irreversible cerebral damage and jeopardize neurodevelopment. Deciding inappropriately however, to operate, can

induce serious morbidity as numerous serious complications of shunt implantation have been described (Drake and Saint-Rose, 1995). Defining the right indication and the right moment for such a procedure is, therefore, very important. Previous studies have shown that in diagnosing progressive hydrocephalus,

Table 2. Number of the initially not-operated and operated patients with normal and raised anterior fontanelle pressure on entering the study.

	not-operated	operated	
normal AFP	6	1	7
raised AFP	8	16	24
TOTAL	14	17	31

Table 3. Number of not-operated and operated patients at the end of the follow-up in relation to normal or raised anterior fontanelle pressure on entering the study.

	not-operated	operated	
normal AFP	5	2	7
raised AFP	5	19	24
TOTAL	10	21	31

clinical signs are often unreliable and sometimes misleading (Kirkpatrick *et al.*, 1989; Hanlo *et al.*, 1995). In this respect, the most common clinical signs in relation to progressive hydrocephalus and raised ICP have been investigated. When an infant with hydrocephalus is admitted with a combination of progressive ventricular dilatation, rapidly increasing head circumference, pulsatile tense fontanelle, sunset phenomenon, vomiting, and impaired consciousness, the patient suffers from raised ICP and shunt implantation or revision will always be performed. When clinical signs are less clear however, additional monitoring of intracranial dynamics can provide important information.

This present study of hydrocephalic infants revealed that the average mental development outcome was approximately 20% lower in the not-operated group with raised ICP levels than

in both the not-operated group with normal ICP levels and the operated group with pre-operatively raised ICP. As the clinical signs in the not-operated group with raised ICP, were not essentially different from those in the operated group with raised ICP, the additional value of non-invasive ICP monitoring is suggested. In patients with raised AFP on entering the study, who were not operated on initially because of dubious clinical signs, but were operated at a later stage because of suspected progressive hydrocephalus, with decreased intracranial compliance, outcome reached the level of normal for age. This suggests that cerebral damage in progressive hydrocephalus can be reversible, even when surgical treatment is delayed in time. Postponing surgical intervention in the cases of abnormal ICP and mild progressive hydrocephalus may therefore be justified, if a careful follow-up is ensured. If, however, ICP levels are persistently abnormal during follow-up, even when clinical signs remain inconclusive, the findings of this study suggest that shunt implantation should be performed.

Conclusion. The decision to shunt or not to shunt is a difficult one. Inter-individual variations between ICP and intracranial compliance do exist, especially in children (Gooskens *et al.*, 1985a). Moreover, other factors, such as cerebral anatomical anomalies and motor deficits, which accompany the hydrocephalic condition, also determine mental development outcome in these infants (Dennis *et al.*, 1981; Hanigan *et al.*, 1991).

An observational study with a rather small number of patients does not allow definite conclusions, but the data of this present study suggest that in infantile hydrocephalus with raised AFP, even when clinical signs are less clear, neurodevelopment benefits from a cerebrospinal fluid diversion procedure. AFP monitoring can, therefore, be of great value.

CHAPTER 8

SUMMARY AND GENERAL DISCUSSION

Hydrocephalus can be defined as an abnormal increase in cerebrospinal fluid (CSF), within the skull, caused by an imbalance between production and absorption, with pathological consequences for the periventricular brain tissue (Aronyk, 1993). This definition does not include hydrocephalus due to primary atrophy of the brain ('ex vacuo').

The diagnosis of progressive infantile hydrocephalus can sometimes be difficult to make and the clinical choices of treatment, as to whether to operate or not, are not always obvious. The differentiation between hydrocephalus that will compensate or arrest in due course, without causing significant cerebral damage, and slowly progressive hydrocephalus, inducing serious neurological deficit, is often hard to make, based only on clinical signs and symptoms (McLone and Partington, 1993). Abnormal increase of CSF, can lead to progressive ventricular dilatation and increase in intracranial pressure (ICP), depending on the compliance of the brain and the skull of the infant. The main goal in treating hydrocephalus is to decrease ICP by means of CSF diversion, thereby restoring the intracranial dynamic balance. The importance of measuring the ICP in childhood hydrocephalus has already been suggested in previous studies.

This thesis represents the results of a study, which is concerned with whether ICP monitoring can be considered a reliable diagnostic tool and thus leads to an improvement in the treatment and long-term prognosis of infantile hydrocephalus.

The ICP in this study was measured non-invasively, by means of anterior fontanelle pressure (AFP) measurements. The AFP measurements were related to transcranial Doppler (TCD) investigations. Furthermore, they were related to clinical signs of progressive hydrocephalus and the corresponding choice of treatment, CSF volume, brain tissue myelination and neurodevelopment.

In this chapter, the following items in relation to the clinical management of infantile hydrocephalus are discussed: (1) the role of CSF pressure, (2) anterior fontanelle pressure measurement, (3) transcranial Doppler investigations, (4) MRI examination, (5) raised ICP and outcome, and (6) future research considerations.

The role of CSF pressure

In hydrocephalus, the accumulation of CSF results in an increase of CSF volume. The volume and pressure of the CSF are mutually dependent (Ryder *et al.*, 1953). This relationship, between CSF volume and CSF pressure, is graphically illustrated by the pressure/volume curve (Shapiro *et al.*, 1980). The slope of the curve ($\Delta V / \Delta P$), reflecting intracranial compliance, is age-dependent and shows considerable inter-individual variation (Gooskens *et al.*, 1985b; Shapiro *et al.*, 1985). The intracranial compliance of a neonate can be large or, in other words, the CSF pressure, or ICP, increases initially relatively little in response to a significant increase in CSF volume.

With rising CSF pressure, the cerebral perfusion pressure (CPP: mean blood pressure - ICP) changes, depending on the cerebral autoregulation. To detect the effect of raised ICP on cerebral haemodynamics, and possibly the CPP, the Doppler ultrasound technique has been

applied in several studies. An important reduction of the cerebral blood flow (CBF), causing brain parenchymal damage, has been registered in infantile hydrocephalus, with improvement of the CBF, after shunt implantation.

The increase of the CSF lactate/pyruvate ratio with a decreasing CPP, is a metabolic effect of raised ICP in hydrocephalic children, restoring the ratio to a more normal level following CSF drainage (Raisis *et al.*, 1976).

Furthermore, as has been suggested by Van der Knaap *et al.* (1991), the process of myelination can be adversely effected by increased ICP in infantile hydrocephalus.

Anterior fontanelle pressure measurement

Crucial to the treatment of progressive hydrocephalus with increased ICP, is CSF diversion, either by shunt implantation or third ventriculostomy, to decrease ICP. Since shunt implantation is associated with serious complications, the indication for treatment must be thoroughly evaluated (Drake and Saint-Rose, 1995). The moment of treatment is also an important issue and is sometimes difficult to determine. The most common clinical signs of raised ICP in infants, such as: tense fontanelle, scalp vein distension, sunsetting or loss of upward gaze, distal diplegia, splayed sutures, pupillary changes, vomiting, behaviour changes and impaired consciousness, are often unreliable or misleading. Based on clinical signs alone, therefore, it can be difficult to decide whether or not to operate. Additional information on intracranial dynamics in infantile hydrocephalus can be obtained by means of ICP monitoring. Due to the risks of invasive ICP measurements in infants, several non-invasive methods, such as anterior fontanelle pressure measurements, have been developed and applied.

First of all, the present study evaluates (1) the reliability of AFP measurements (*Chapter 2*) and (2) the relationship between the AFP and clinical signs in infantile hydrocephalus (*Chapter 3*). For AFP measurements the Rotterdam Teletransducer (RTT) was used.

The reliability of the RTT (Chapter 2). Both in vitro and in vivo investigations were carried out to evaluate the performance of the RTT under several conditions.

Initially, the effect of the different physical qualities of the RTT were investigated, using a specially developed, sensitive calibration device. The in vitro measurements were performed under ideal laboratory conditions and in so-called, simulated clinical situations. From these measurements it was concluded, that a thermal stabilization time, defined as the time necessary for the output of the device to stabilize, after being switched on, of at least three hours, is necessary to avoid serious drift in the measurement. The RTT can be calibrated accurately, with an average pressure difference between the calibration pressure and the RTT pressure of only 0.3 mmHg. The temperature difference between the membrane of the calibration device and the fontanelle had no effect on the AFP measurement. In a simulated clinical condition, it was found that a considerable measurement error (-2.6 up to 1.3 mmHg) could occur by manipulation of the transducer. Secondly, the validity of the AFP measurements was evaluated, by comparing them to simultaneous intraventricular pressure

(IVP) measurements. Correlations between AFP and IVP varied from 0.96 to 0.98. In all these measurements, as the pressure increased, AFP exceeded IVP (offset of 3 to 4 mmHg). It can be concluded, that the RTT proved to be an accurate device for ICP monitoring, if extended operating procedures are considered. Further hardware improvements to reduce thermal stabilization time and to improve gain and offset adjustment procedures will increase its reliability even more.

The relationship between AFP and clinical signs (Chapter 3). Using a standardized protocol, the relationship between long-term AFP measurements and clinical signs was investigated in 37 infants with hydrocephalus. The decision as to whether or not to operate was based on clinical signs alone, AFP values were not taken into account.

There was an overall difference between the not-operated and operated (pre-operative) group, and also between the pre-operative and postoperative group, regarding both the AFP measurements and clinical signs. Almost all of the pre-operative AFP values were increased and the higher AFP values (>18 mmHg) were also observed most often in the pre-operative measurements. Shunt implantation had a distinct effect on both the presence of clinical signs and the AFP levels. The direct correlation (*phi*) between the individual clinical signs and the actual AFP levels however, was low for most of the signs (*phi* = 0.15 - 0.41). The clinical sign, 'tense fontanelle', showed the best correlation with the AFP levels (*phi* = 0.75). Furthermore, using logistic regression analysis, no combination of clinical signs could be found, to provide a reliable prediction of the mean AFP.

As far as the known inter-individual variations of the clinical effect of increased intracranial pressure are concerned, the present study also examined the value of pathological pressure variables, in relation to clinical signs and mean AFP. These variables, such as A-waves and frequent B-waves, are the result of the individual's limited intracranial compliance. In the case of low compliance, the patient is no longer able to buffer small volume changes and is therefore, unable to prevent the development of pressure increase and pressure variables. In the present study, the pathological A-waves occurred only in the presence of raised AFP, a situation in which considerably more frequent B-waves were also observed.

The following conclusions can be drawn from the study results: (1) the relationship between the clinical condition of the hydrocephalic infant and the AFP is often not very obvious; (2) clinical signs of raised ICP, in infantile hydrocephalus, are not very reliable and additional ICP monitoring can therefore, provide valuable information in patients, with dubious neurological manifestations of progressive hydrocephalus; (3) further investigation of the pathological pressure variables in infants is necessary, in order to disclose their value in detecting deteriorating intracranial dynamics.

Transcranial Doppler investigations

The presence of an open fontanelle allows non-invasive ICP assessment, by means of AFP measurement. Since changes in ICP have their effect on cerebral haemodynamics, especially CPP, a non-invasive evaluation of the cerebral circulation, by means of Doppler ultrasonography, is being widely used in infants and children with hydrocephalus. If the

fontanelle has already closed, transcranial Doppler (TCD) investigations, measuring changes in blood flow velocities due to increased ICP, could provide additional information on intracranial dynamics.

The different aspects of the blood flow velocity (systolic peak flow velocity (SPFV), end-diastolic flow velocity (EDFV) and mean flow velocity (MFV)) have been determined. The relationship between the most common ratios (Pulsatility Index (PI); Resistance Index (RI)) and increased ICP have been assessed. In previous studies, no common opinion was reached however, on the value of these indices in predicting raised ICP.

In this thesis, (1) the relationship between AFP and transcranial Doppler variables (*Chapter 4*) and (2) a new Doppler index: the Trans Systolic Time (*Chapter 5*) are discussed.

The relationship between AFP and TCD (Chapter 4). A total of 15 pre- and postoperative long-term measurements were examined, in order to study the effect of shunt implantation, on the AFP values, in relation to the TCD variables. Although all pre-operative AFP values were abnormal, only 6 PI values and 5 RI values were abnormal. Postoperatively, the AFP decreased by almost 50%, the PI by 25% and the RI by 13%. There was however, no direct correlation between the AFP values and the TCD variables in the pre- and postoperative measurements. In one measurement, there was even an increase in PI and RI, whilst AFP decreased considerably. Another 22 continuous, simultaneous AFP/TCD measurements were investigated for the influence of substantial pressure variations on the TCD variables. It appeared that, in 21 measurements, the SPFV and MFV, and in 16 measurements, the EDFV, correlated significantly with the AFP values. The commonly used PI and RI ratios, showed negative or poor correlations.

The difference between these findings and the observations described in previous studies, in which has been suggested that the current Doppler indices are of value in predicting raised ICP, is probably due to the fact that in the present study, long-term, instead of short-term, measurements were evaluated. In this way the important variations in ICP are accounted for.

The conclusion must therefore be, that the current Doppler indices, PI and RI, are not reliable for monitoring intracranial dynamic responses, in the case of raised ICP and neither do they provide sufficient data, which could facilitate the decision, whether or not to perform shunt implantation in infantile hydrocephalus. More specific research on Doppler waveform analysis, in long-term measurements, can provide a valuable assessment of cerebral perfusion changes in the individual patient. In this way, the hydrocephalic patient at risk, can be detected and an attempt can be made, to prevent secondary cerebral ischaemic insult.

A new Doppler index: the Trans Systolic Time (Chapter 5). Since PI and RI ratios have certain drawbacks regarding their relationship to variations in ICP, a new Doppler index, the Trans Systolic Time (TST; a time related index), has been developed. This TST is defined as the width of the systolic peak at the level of $V_{tst} = (V_{ps} + V_{ed})/2$ (V: flow velocity; ps: peak systole; ed: end-diastole; *Chapter 5, Figure 5*). The development of the TST is based on physical qualities, such as capacitances and resistances, incorporated into a hydrodynamic model and its electrical analogue. From these models, a mathematical description of the up- and downstroke of the TCD waveform is derived. Since the upstroke is considered to be

constant in infantile hydrocephalus, changes in the shape of the TCD envelope are reflected primarily in the shape of the downstroke. Mathematically, the shape of the exponential downstroke curve, is determined primarily by the cerebrovascular resistance. Extracranial factors have less impact on the shape of the downstroke curve, than on the actual blood flow velocity values, represented in the PI and RI ratios. The shape of the TCD envelope, especially the downstroke, is reflected in the TST. Compression of the venous vascular system, induced by increased ICP, results in an increase of the cerebrovascular resistance and thus a decrease of the TST. Clinical observations in hydrocephalic infants confirm these findings. The present study showed that the TST increased significantly, with a drop in ICP, following adequate shunting.

Compared to PI and RI, the TST seems to reflect more specifically, the physical properties of the intracranial system. In this respect, theoretically, a simple waveform analysis, such as the TST, can lead to an improved evaluation of the effect of ICP changes on the CBF. Clinical application of a waveform analysis such as the TST, needs further investigation to define its value, in relation to the treatment decision.

MRI examination

Since the introduction of the MRI technique, it has been possible, not only to produce more detailed images of the intracranial structures, but also to study the different aspects of brain tissue characteristics. In this respect, cerebral myelination patterns, i.e. the process of brain maturation, have been described in both normal and hydrocephalic children (Barkovich *et al.*, 1988; Van der Knaap *et al.*, 1990, 1991; Squires *et al.*, 1995). In infantile hydrocephalus, Van der Knaap *et al.* (1991), showed a highly significant correlation between myelination and psychomotor development. No correlation was found however, between the size of the CSF volume and neurodevelopmental performance or between CSF volume and myelination. It is probable, therefore, that there is a relationship between raised ICP and delayed brain maturation.

The effect of ICP on myelination (Chapter 6). Nineteen infants with hydrocephalus were followed-up by MRI, neurodevelopmental testing (NDT) and AFP measurement. In 16 patients, with confirmed progressive hydrocephalus, shunt implantation was performed. In three patients with mild or non-progressive hydrocephalus, the decision regarding surgical intervention was postponed.

There was a gradual decrease in CSF volume (average decrease at 6 weeks postoperatively: 10%; at 6 months: 22%) after shunt implantation. The average drop in mean AFP level, at 6 weeks postoperatively, was 55%. Postoperatively, both the degree of myelination and NDT score increased equally and substantially.

The size of the CSF volume showed a poor correlation with the mean AFP, the degree of myelination and the NDT scores. There was, on the other hand, a significant correlation between the mean AFP and the degree of myelination ($r = 0.67$) and also between the mean AFP and the NDT scores ($r = 0.70$). The high correlation ($r = 0.80$) between the myelination and NDT scores was also confirmed in this study. By means of multiple regression analysis,

it was calculated that 69% of the variation in NDT was related to the influence of mean AFP and myelination.

A more long-term follow-up (mean: 27 months) showed a significant correlation between the progress of myelination and the developmental level ($r = 0.78$). Most of the children with a severely delayed pre-operative degree of myelination, showed a recovery of myelination, following adequate CSF drainage.

It can be concluded from this study that, (1) raised ICP is related to the developmental outcome, through the process of myelination, but cannot account entirely for the delay in myelination and neurodevelopment; (2) the delay in myelination can be (partially) reversible; (3) CSF volume is of minor importance regarding neurodevelopment. Further research is needed to disclose other factors, that influence the process of myelination and establish the prognostic value of the early progress of myelination, for truly long-term outcome, i.e. school performance.

AFP measurements and treatment decision

Based on clinical signs alone, it remains quite difficult to decide whether or not to perform shunt implantation or revision in infantile hydrocephalus. An inappropriate decision, not to operate, can jeopardize neurodevelopment; on the other hand, an unnecessary operation can cause serious morbidity, due to the various shunt complications in infants. The important issue of defining the right indication and right moment for a CSF diversion procedure was discussed in the following chapter.

The relationship between raised ICP, shunt implantation and outcome (Chapter 7). To assess the value of AFP measurements in relation to the treatment decision, 31 hydrocephalic infants, without focal parenchymal damage on MRI, were examined. The treatment decision was taken on clinical grounds, independently from the AFP measurements. Only the mental development outcome was determined, because patients with spina bifida (inherent motor deficit) were also included in the study. All operated patients, excepting one, showed a pre-operative increased ICP, which normalized after shunt implantation. The clinical signs in the not-operated patients, with raised ICP, were not essentially different from those in the operated group. These not-operated patients, with a persistently raised ICP however, showed an average of more than 20% reduced mental development outcome score at the end of follow-up (average: ± 20 months), in comparison with both the not-operated patients with normal ICP and the operated patients with adequate shunt function. All of the three patients with raised ICP on entering the study and with dubious clinical signs, who were operated at a later stage, showed an adequate mental development outcome at the end of follow-up.

Although the patient numbers in this study are rather small, we conclude, that neurodevelopment in hydrocephalic infants with persistently abnormal ICP values, even when clinical signs are less evident, can benefit from a CSF diversion procedure. Non-invasive ICP monitoring can, therefore, be of great value.

Future investigations

Future research should be aimed at effective functional recovery in infantile hydrocephalus by the improvement of treatment, through advanced diagnostic procedures. Systematic studying of hydrocephalic infants as well as the use of animal models (MacAllister, 1985; Jones and Bocknall 1987; Harris, 1992; Matsumoto *et al.*, 1994) will provide a better understanding of intracranial hydrodynamics.

Different techniques are available for studying the various morphological, physiological and clinical variables. Cine-MRI, for instance, visualizes the mobility of the ventricular walls, which is related to the buffer capacity or compliance of the CSF spaces (Naidich *et al.*, 1993). MRI also facilitates the visualization and quantification of the intracranial CSF flow, and a reliable quantification of the flow through a shunt system is likely to become a reality in the near future (Naidich *et al.*, 1993). In this way this non-invasive diagnostic procedure could also be helpful in detecting shunt dysfunction.

Extensive (computerized) ICP waveform analysis in infants, and its relation to cerebral perfusion pressure (CPP) changes (Chopp and Portnoy, 1980; Portnoy *et al.*, 1982; Rosner and Becker, 1984; Avezaat and Eijndhoven, 1986; Cardia *et al.*, 1987; Takizawa *et al.*, 1987; Robertson *et al.*, 1989; Czosnyka *et al.*, 1994a; Price *et al.*, 1994; Zabolotny *et al.*, 1994; Hanlo *et al.*, 1995) and CSF outflow resistance, by means of invasive infusion techniques (Marmarou *et al.*, 1975; Gooskens *et al.*, 1985b; Børgesen and Gjerris, 1987; Czosnyka *et al.*, 1994b), can provide valuable information on intracranial dynamics and the need for CSF diversion in hydrocephalus.

Combined cerebral blood flow (CBF; using color Doppler techniques) and ICP measurements could identify those patients with decreased circulatory reserve and limited intracranial compliance, who are at risk of a secondary ischaemic insult, as a consequence of raised ICP. The role of microcirculatory failure in the damage of the developing brain in hydrocephalus has to be further investigated by CBF studies, using single photon emission computed tomography (SPECT) (Sato *et al.*, 1991; Shinoda *et al.*, 1992).

Apart from the development of more specific Doppler indices, such as the Trans Systolic Time, for monitoring the effect of raised ICP on cerebral haemodynamics, advanced TCD signal analysis has to be further developed (Czosnyka *et al.*, 1994c; Keunen *et al.*, 1994).

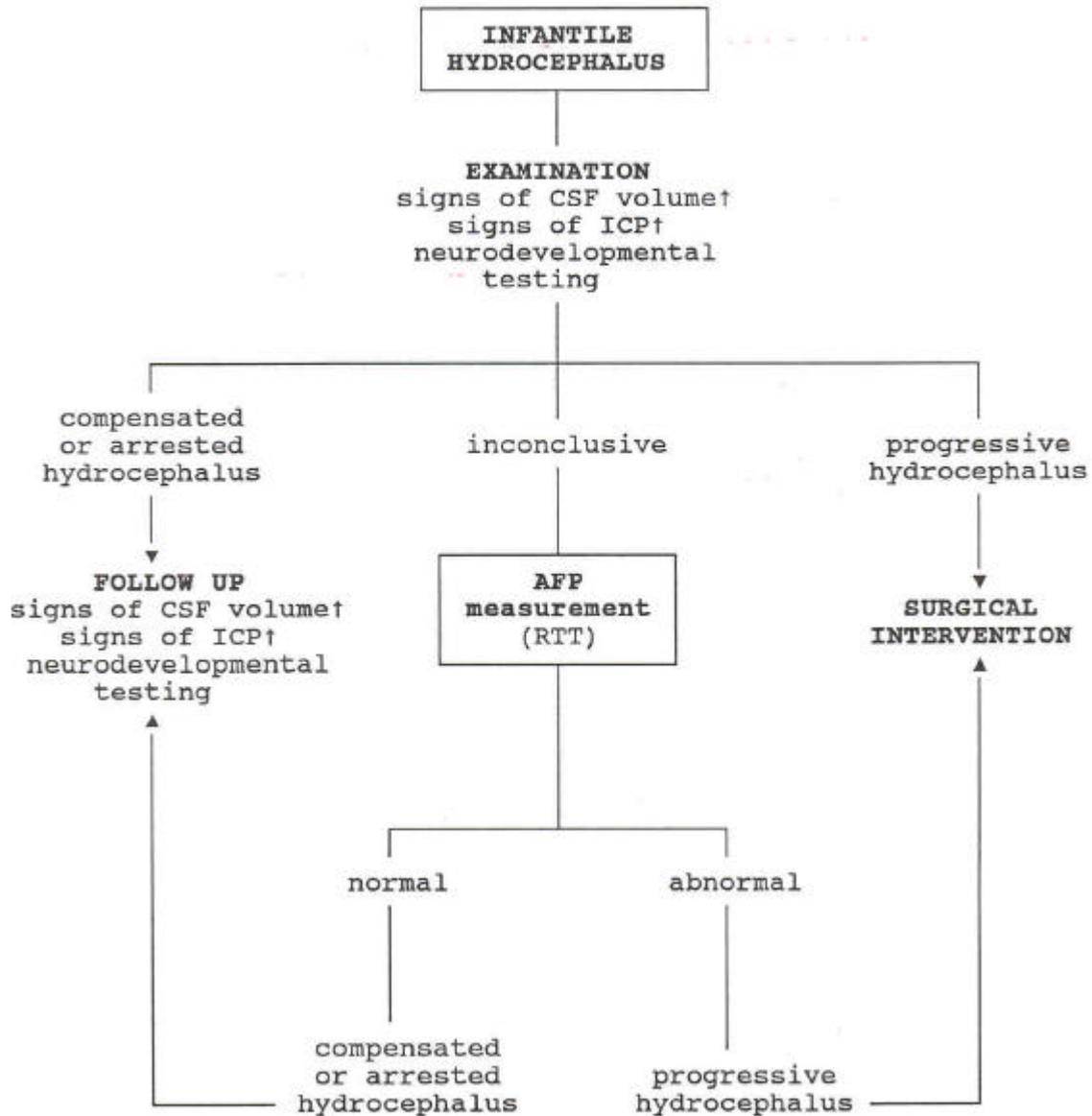
More specific metabolic processes in hydrocephalus, can be studied by MR spectroscopy (MRS) and positron emission tomography (PET) (Shirane *et al.*, 1991; Da Silva *et al.*, 1994). Future research will also have to focus on the relationship between CSF dynamics, CBF and cerebral metabolism in hydrocephalic children.

Relating the diagnostic procedures, mentioned above, to other neurophysiological investigations, such as evoked potentials (De Vries *et al.*, 1990) and EEG registrations (Van Huffelen, 1974; Watanabe *et al.*, 1984), also offers valuable prospects.

Last but not least, treatment strategy has to be assessed by a further on-going evaluation of long-term outcome in childhood hydrocephalus, using standardized neurological examination and validated neurodevelopmental testing. It is only possible, by thoroughly studying and documenting the pathophysiological changes, as a result of hydrocephalus in young children,

that the effects of the different treatment strategies, whether to operate or not, can be adequately assessed.

Guidelines for assessing the treatment of infantile hydrocephalus



*Compensated: no surgical intervention; arrested: after surgical intervention.
AFP: anterior fontanelle pressure; TCD: transcranial Doppler.*



SAMENVATTING

Hydrocephalus is in deze studie gedefinieerd als een abnormale toename van de liquor cerebrospinalis binnen de schedel, veroorzaakt door een verstoring van het evenwicht tussen aanmaak en resorptie van de liquor. Deze definitie sluit een hydrocephalus door weefselverlies (hersensatrofie) uit.

Het stellen van de diagnose progressieve hydrocephalus bij jonge kinderen is vaak moeilijk en het te volgen beleid hierbij, wel of niet opereren, is niet altijd duidelijk. Het onderscheid tussen een gecompenseerde hydrocephalus, zonder aantoonbare cerebrale schade en een langzaam progressieve hydrocephalus, met neurologische deterioratie, is op basis van klinische symptomen moeilijk te maken. Abnormale toename van het liquorvolume leidt tot ventrikeldilatatie en een stijging van de intracraniele druk (ICD). Bij de behandeling van hydrocephalus is verlaging van de ICD, middels liquordrainage en herstel van het intracraniele dynamische evenwicht van groot belang. In dit proefschrift worden de resultaten besproken van een studie, waarbij werd onderzocht of niet-invasieve ICD-meting een betrouwbare vorm van diagnostiek is en kan bijdragen tot een verbetering van de behandeling bij jonge kinderen met hydrocephalus. In deze studie werden ICD-metingen gerelateerd aan de belangrijkste klinische symptomen van progressieve hydrocephalus, transcranieel Doppler (TCD) onderzoek, myelinisatie van de hersenen en neuropsychologisch onderzoek.

Hoofdstuk 1 geeft een algemene inleiding op het in dit proefschrift beschreven onderzoek. Een kort historisch overzicht over de diagnostiek en behandeling van hydrocephalus wordt gegeven. Vervolgens worden de onderdelen van de studie apart belicht (fontaneldrukmeting: methode en kliniek; transcranieel Doppler onderzoek: signaalanalyse en de relatie met de ICD; myelinisatie van de hersenen: relatie tussen ICD and outcome). Hierna worden de afzonderlijke doelstellingen van het onderzoek geformuleerd:

- validatie van de Rotterdam Teletransducer als methode voor fontaneldrukmeting.

- bepalen van de relatie tussen de fontaneldruk en de klinische symptomen bij jonge kinderen met hydrocephalus.
- bepalen van de relatie tussen de fontaneldruk en de Doppler indices, om de betrouwbaarheid van deze indices bij het voorspellen van de ICD vast te stellen.
- bepalen van het effect van verhoogde ICD op de myelinisatie en neuropsychologische ontwikkeling bij jonge kinderen met hydrocephalus.

In *hoofdstuk 2* wordt de betrouwbaarheid van de Rotterdam Teletransducer (RTT) voor fontaneldrukmeting onderzocht. De verschillende fysische kwaliteiten van de RTT werden bestudeerd met behulp van een speciaal ontwikkeld calibratie-apparaat. Bij de in vitro experimenten bleek dat de opwarmperiode van de RTT, om belangrijke zero-drift te vermijden, tenminste drie uur bedraagt. De RTT bleek eenvoudig te calibreren. Manipulatie van de transducer, bijvoorbeeld bij positioneren op de fontanel, kan echter leiden tot een meetfout van een enkele mmHg. Om de validiteit van fontaneldrukmetingen te onderzoeken werden deze metingen vergeleken met simultane intraventriculaire metingen. De correlaties tussen deze drukmetingen varieerden van 0.96 tot 0.98.

In *hoofdstuk 3* wordt de relatie tussen de fontaneldruk en de individuele klinische symptomen bij hydrocephalus beschreven. Volgens een protocol werden 37 jonge kinderen met hydrocephalus onderzocht. De beslissing om wel of niet te opereren was alleen gebaseerd op klinische symptomen, de drukmeting werd hierbij buiten beschouwing gelaten. Er was een verschil tussen de niet geopereerde en geopereerde groep, en tussen de pre-operatieve en postoperatieve groep, met betrekking tot zowel de gemiddelde fontaneldruk als de klinische symptomen. Shuntimplantatie had een duidelijk effect op zowel de aanwezigheid van klinische symptomen als de hoogte van de fontaneldruk. De directe correlatie tussen de meeste individuele klinische symptomen en de gemiddelde fontaneldruk of drukvariabelen (A-golven, B-golven) was echter laag. Het klinische symptoom 'gespannen fontanel' gaf de

beste correlatie met de hoogte van de fontaneldruk ($\phi = 0.75$). Middels logistische regressie-analyse kon geen combinatie van symptomen worden gevonden, die een betrouwbare voorspelling van de gemiddelde fontaneldruk of ICD kon geven. Klinische symptomen toegeschreven aan verhoogde ICD bij hydrocephalus bij jonge kinderen, blijken een matige weerspiegeling te zijn van de werkelijke ICD. Fontaneldrukmeting kan dan ook belangrijke toegevoegde informatie verschaffen bij patiënten zonder evidente neurologische manifestaties van progressieve hydrocephalus.

In *hoofdstuk 4* wordt de relatie tussen fontaneldrukmetingen en transcraaneel Doppler (TCD) onderzoek bij kinderen met hydrocephalus bestudeerd. Na shuntimplantatie bleek er een gemiddelde afname te bestaan van de fontaneldruk van 50%. De TCD-indices namen eveneens af na shuntimplantatie, de Pulsatility Index (PI) verminderde met 25% en de Resistance Index (RI) met 13%. Er bestond echter geen significante correlatie tussen waarden van de fontaneldruk en PI of RI in de pre- en postoperatieve metingen. Om de directe relatie tussen de fontaneldruk en de TCD-variabelen te onderzoeken, werden individuele simultane fontaneldruk/TCD-metingen geanalyseerd. In de meeste metingen bestond een significante correlatie tussen de fontaneldruk en de 'systolische bloedstroomsnelheid', de 'diastolische bloedstroomsnelheid' en de 'gemiddelde bloedstroomsnelheid'. De correlaties van de fontaneldruk met de PI en RI waren slecht of zelfs negatief. Veranderingen in PI of RI waren vaak niet parallel aan de verandering in de fontaneldruk. De meest gebruikte TCD-indices (PI en RI) blijken dus geen betrouwbare maten te zijn voor de intracraniale druk. Meer specifieke analyse van het Doppler signaal is noodzakelijk om de intracraniale dynamiek te evalueren en daarmee secundaire cerebrale ischaemische schade te voorkomen.

In *hoofdstuk 5* wordt een theoretisch model voor een nieuwe, tijd gerelateerde en meer specifieke Doppler index, de 'Trans Systolic Time' (TST), besproken. De TST is gedefinieerd als de breedte van de systolische piek op het niveau $V_{tst} = (V_{ps} + V_{ed})/2$ (*Hoofdstuk 5, Figuur 5*). De ontwikkeling

van de TST is gebaseerd op fysische componenten, zoals condensatoren en weerstanden, geïncorporeerd in een hydrodynamisch model en zijn elektrische analogon. Middels deze modellen werd een mathematische beschrijving van het TCD-sigitaal verkregen. De exponentiële vorm van de 'downstroke' wordt voornamelijk bepaald door de cerebrovasculaire weerstand. Extracraniale factoren, zoals de hartfrequentie, hebben minder invloed op de vorm van de 'downstroke'-curve, dan op de feitelijke bloedstroomsnelheden, die gebruikt worden in de PI- en RI-berekening. Een afspiegeling van de vorm van het TCD-sigitaal wordt weergegeven in de TST. Een toename van de cerebrovasculaire weerstand als gevolg van verhoogde ICD, leidt tot een afname van de TST. Klinische observaties bevestigen deze theoretische bevindingen. In vergelijking met de PI en RI, lijkt de TST een meer specifieke weergave van de fysische eigenschappen van het intracraniale systeem. Klinische toepasbaarheid van de TST behoeft nader onderzoek.

In *hoofdstuk 6* wordt het effect van fontaneldruk of ICD op de myelinisatie van de hersenen beschreven. Jonge kinderen met hydrocephalus werden systematisch gevolgd met MRI, neuropsychologisch onderzoek (NPO) en fontaneldrukmeting. Bij patiënten met een progressieve hydrocephalus werd een shuntimplantatie verricht. Er trad een geleidelijke afname van het ventrikelvolume op (gemiddeld 22% na 6 maanden). De gemiddelde afname van de fontaneldruk na 6 weken bedroeg 55%. Postoperatief nam zowel de mate van myelinisatie als de NPO-score aanzienlijk toe.

De grootte van het ventrikelsysteem correleerde matig met de gemiddelde fontaneldruk, de mate van myelinisatie en de NPO-score. De hoge correlatie ($r = 0.80$) tussen de myelinisatie en de NPO-score werd in deze studie bevestigd. Bovendien bestond er een significante correlatie tussen de gemiddelde fontaneldruk en de mate van myelinisatie ($r = 0.67$) en tussen de gemiddelde fontaneldruk en de NPO-score ($r = 0.70$). Middels multiple regressie analyse werd berekend dat 69% van de variatie in NPO-score het gevolg was van de invloed van de fontaneldruk en de myelinisatie.

Na een gemiddelde postoperatieve follow-up periode van 27 maanden lieten de meeste kinderen met een pre-operatieve vertraagde myelinisatie, een herstel van de myelinisatie zien. Uit deze studie blijkt dat verhoogde ICD correleert met de outcome (neuropsychologische ontwikkeling) op langere termijn, via het proces van de myelinisatie. Verhoogde ICD alleen is echter niet de enige verklaring voor een vertraagde myelinisatie en neuropsychologische ontwikkeling bij kinderen met hydrocephalus. Onderzoek naar andere factoren die het proces van myelinisatie bij kinderen met hydrocephalus kunnen beïnvloeden is noodzakelijk.

In *hoofdstuk 7* wordt de relatie tussen verhoogde ICD, shuntimplantatie en outcome bestudeerd. 31 Kinderen met hydrocephalus werden in de studie opgenomen. De beslissing om wel of niet te opereren werd gebaseerd op grond van klinische symptomen alleen, onafhankelijk van de fontaneldruk. Alleen de mentale outcome, en niet de motorische, werd gescoord, omdat ook kinderen met spina bifida (inherente motorische uitval) in de studie werden opgenomen. De klinische symptomen bij de niet geopereerde patiënten met verhoogde fontaneldruk of ICD, waren niet wezenlijk verschillend van de symptomen bij de geopereerde groep. Deze niet geopereerde patiënten, met persisterende verhoogde ICD, toonde een gemiddeld 20% lager mentaal ontwikkelingsniveau aan het eind van de follow-up periode, in vergelijking met zowel de niet geopereerde patiënten met een normale ICD als met de geopereerde groep met adequate liquordrainage. Ondanks het feit dat het patiëntenaantal in deze studie beperkt is, kan gesteld worden dat bij jonge kinderen met hydrocephalus en persisterende verhoogde ICD-waarden, zonder evidente neurologische manifestaties, liquordrainage geïndiceerd is. Daarom kan niet-invasieve ICD-meting hierbij een toegevoegde waarde hebben.

Hoofdstuk 8 betreft een algemene discussie met betrekking tot in de voorgaande hoofdstukken beschreven onderzoeksresultaten en conclusies.

Gesteld kan worden dat:

- fontaneldrukmeting met behulp van de Rotterdam Teletransducer een betrouwbare methode is om de ICD te bepalen, mits specifieke gebruiksvoorwaarden in acht worden genomen.
- symptomen van verhoogde ICD vaak onbetrouwbaar zijn, en niet altijd specifiek genoeg voor het bepalen van een shunt-indicatie bij kinderen met hydrocephalus.
- de meest gebruikte Doppler indices niet geschikt zijn om de ICD te voorspellen, en derhalve niet zondermeer gebruikt kunnen worden voor het stellen van een shunt-indicatie. Een meer bruikbare Doppler index zou de Trans Systolic Time kunnen zijn; de klinische toepassing hiervan behoeft nader onderzoek.
- er een duidelijke relatie bestaat tussen de hoogte van de ICD en de mate van myelinisatie van de hersenen en neuropsychologische ontwikkelingscore bij kinderen met hydrocephalus. Liquordrainage lijkt geïndiceerd bij kinderen met hydrocephalus zonder duidelijke neurologische manifestaties, maar met een persisterende verhoogde ICD.



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CURRICULUM VITAE

De auteur van dit proefschrift is geboren op 25 juli 1958 te Eindhoven. Na het behalen van het Gymnasium- β diploma (Van der Putt Lyceum, Eindhoven), studeerde hij twee jaar Psychologie aan de Rijksuniversiteit te Utrecht en vanaf 1978 studeerde hij Geneeskunde aan de Rijksuniversiteit te Utrecht. Op 29 augustus 1986 behaalde hij zijn artsexamen. Van 1987 tot 1992 volgde de opleiding tot neuroloog (Opleider: Prof.Dr J. van Gijn). Tijdens zijn opleiding tot neuroloog participeerde hij in het onderzoeksprogramma 'Cerebrale Ontwikkelingsstoornissen' van de afdeling Kinderneurologie van het Wilhelmina Kinderziekenhuis te Utrecht (Hoofd: Prof.Dr J. Willemse). Gedurende één jaar (1992-1993) deed hij full-time onderzoek op het gebied van hydrocephalus op de afdeling Kinderneurologie (Onderzoeksleider: Dr R.H.J.M. Gooskens). Vanaf 1 januari 1993 is hij in opleiding tot neurochirurg (Opleider: Prof.Dr C.A.F. Tulleken). De stage algemene heelkunde werd van 1 januari 1994 tot 1 januari 1995 volbracht in het Diaconessenhuis te Utrecht (Opleider: Dr P. Leguit).



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Jan Hanlo

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