Listening to the brain of the newborn by the Doppler Method

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The clinical assessment of the arterial cerebral circulation

by Doppler investigation in neonates.

"There are several ways
to observe the brain functions.
Let us consider the Doppler method as a stethoscope for the brain" .

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All my gratitude

To my mother and my father who made so many efforts to make

possible my studies in Medicine.

And to all parents who did the same for their children.

" on a Christmas day, ready for the presents..."

Content of the manuscript

This chapter approaches the technical aspects, the physical principles, the description of the sonogram, the different steps for analysis and records, and the normal values.

This chapter is devoted to the pathophysiology of brain ischaemia and hypoxia in neonates; to the concepts of neuronal and glial cells alliance, and to the integrity and of all function levels for activities; to the cerebral blood flow autoregulation and the concepts of brain's ischaemia, hypoxia and hypoglycaemia.

This section is related to the effects of acute and chronic respiratory distress on the cerebral blood flow velocities, and also on the relationships between cerebral and extracerebral haemodynamics.

This belongs to the effects of several drugs on the Cerebral Blood Flow Velocities.

This chapter contains a special mention for the ductus arteriosus and cerebral haemodynamics.

It is related to states such as: cerebral edema, significant ventricular dilatation and to the assessment of the intracranial pressure.

It contains issues about the perinatal haemodynamic characteristics of fetal and neonatal growth retardation.

Introduction.

Perinatal brain ischaemia and hypoxia, including their sequelae, are, from a qualitative point of view, an important cause of morbidity or several "difficulties" (failure to thrive, cognitive acquisitions) in early infancy and even later on, and to a lesser extent or mortality.The *morbidity* concerns the motor, visual as well as the cognitivies functions. Hence most of the neonatal research interests are devoted to reduce the incidence of perinatal ischaemia and hypoxia.

There are *several methods of neurological investigations* during the neonatal period. These are as follows:

➔ the clinical examination, including the assessment of general movements ideally recorded by videos;

➔ the imaging techniques combining functional aspects: real-time ultrasounds, magnetic resonance imaging and spectroscopy, positron-emission and single photon emission tomography scans, computerized tomography scans;

➔ the electrophysiology (the EEG and also the visual, auditive and somatosensory evoked potentials);

➔ the near-infrared spectroscopy;

➔ the intracranial pressure monitoring;

➔ all the brain-oriented metabolic investigations;

➔ the Doppler examination of blood flow velocities in arteries and veins;

➔ the transcephalic electrical impedance;

➔ the tissular measurements of glucose, pH and pO2 (in situ).

The most frequently **acquired brain injuries in premature and term infants** are:
the damage or, more precisely, the diseases of white matter, the peri- and -intraventricular haemorrhages, the occlusive vascular disorders, the post-hypoxic encephalopathy. These have often an hypoxic/ischaemic origin due to both local or extracerebral causes owing to the relationships between the intracerebral and the extracerebral haemodynamics aspects (see Chapter II, section 3: The cerebral blood flow autoregulation).

At cellular levels the important parameters are the cerebral deliveries (D) and consumptions (Metabolic Rate) of oxygen (O2) and glucose (G). It is important to monitor the

haemodynamic parameters, because CMRO2, CMRG, CDO2 and CDG are dependent of the arterial concentration of the metabolites, the cerebral blood flow and the coefficient of metabolites extraction as explained further.

Cerebral blood flow is not always well autoregulated in neonates with a respiratory distress syndrome, severe hypoglycaemia or circulatory failure, and this is accounts for a direct influence of extracerebral parameters such as blood pressure, cardiac output, arterial pH and blood gases (pCO2, pO2), arterial contents of oxygen , haemoglobin and glucose, and the therapeutic procedures on the cerebral haemodynamics.

The measurements of cerebral blood flow velocities and derived indices of vascular resistance and perfusion, were progressively introduced as tools for investigations, but not without a significant criticism in the literature . The systemic blood pressure and the cerebral blood flow velocities (CBFV), when matched to other standard methods measuring the cerebral blood flow, are able to estimate or to give a useful index of the CBF.

The Doppler technique can be used as an adjunct to clinical management, particularly for monitoring the cerebral haemodynamics in neonatal intensive care units, provided the five following points are kept in mind:

1. It reflects qualitative circulatory changes, and one should not extrapolate the numeric findings from one study to another.

2. It requires good conditions and good equipment settings for the measurements. In particular, it should be possible to measure systolic, diastolic and mean velocities, as well as acceleration and deceleration times.

3. The best information is obtained from serial (monitoring purpose) than from isolated measurements (diagnostic purpose).

4. It requires to be integrated into the pathophysiology of the patient, and particularly of his brain.

5. As other techniques, it has inter-subject and intra-subject variability.

We will go through these points based on available literature. We will also report our experience extending from 1986 to 1996 concerning 514 patients studied in our neonatal intensive care unit. We aim to provide practical guidelines and norms in clinical settings concerning the care and monitoring of neonatal brain, with the help of the Doppler method. Indeed, although there are fairly good books for adults and children in that field, to our knowledge, there isn't such one for neonates. The references list, as always in a manuscript, had to be stopped at some time. After each chapter, the references claimed by the author have been gathered: every reference numbered is given in details in the end of the manuscript. We apologize to those authors not finding their own work's reference(s) in that list. Any future comments, remarks or observations reported to us will be taken up and shall greatly be appreciated.

Abstract of this monography

- *The Doppler technique is important for the assessment of circulation in Cardiology and in fetal Medicine. We consider the Doppler technique as a stethoscope for the brain that can be used in the intensive neonatal care unit. It requires good conditions and a "good equipment". Pulsed Doppler systems are more accurate than continuous Doppler systems, but finally one may use either. The system should provide the possibility to use pencil-like or flat-type probes. One should be able to measure the best recorded samples of parameters such as i. the systolic and diastolic velocities, both in their anteverse and retroverse phases;ii. the acceleration and deceleration times. The mean velocity and the area under the curve should be displayed (after their calculation, implying the use of the adequate formulas) by the system. As for other techniques, we may find intersubjects and intrasubjects variabilities, but that can be monitored by the system and by the investigator to avoid errors. The knowledge of the physical principles beneath that technique and the integration of that method in the pathophysiology (both intra- and extra-cerebral) of neonates are two strong protectors against mistakes in interpreting the results and in the comparison of results between different authors (see the importance of "F" value whether anatomy or haemodynamic is concerned).*

- **The Doppler technique can be used as an adjunct to clinical management, particularly for monitoring the cerebral haemodynamics in neonatal intensive care units, provided the five following points are kept in mind:**

1. It reflects qualitative circulatory changes, and one should not extrapolate the numeric findings from one study to another. The main reason is the physical principle of the technique.

2. It requires good conditions and good equipment settings for the measurements (see above).

3. The best information is obtained from serial (monitoring purpose) than from isolated measurements (diagnostic purpose).

4. It requires to be integrated into the pathophysiology of the patient, and particularly to circulation, respiration and brain.

- **_The Doppler technique is able to make the diagnosis of presence (or absence) of:_**

1. The cerebral blood flow autoregulation.

2. The mesenteric blood flow autoregulation.

3. The cerebral perfusion homogeneity.

4. The increased or decreased impedance of flow(s).

5. The importance of the shunt through the ductus arteriosus.

6. The neurovegetative haemodynamic variability or stability.

7. An increased intracranial pressure or cerebral perfusion pressure.

8. An effect of a procedure (anaesthesia, surgery, ventilation), a state (respiratory distress, ventricular dilatation), or a pharmacologic intervention

- **_Depending on what is suspected, the Doppler technique should be applied to the best vessels for a given purpose:_** according to the clinical present situation, the clinician will focalise its attention on : i.the most interesting vessels : on one or on both sides for the anterior and middle cerebral arteries, the left common carotid artery, the superior mesenteric artery; ii. And these intracerebral parameters need to be considered (for possibly influencing them) with several extracerebral parameters.

Gathered references claimed in the Introduction (see the details at the end, in the References):

2,3,4,6,7,10,13,16,15,17,20,21,22,23,24,25,26,27,28,29,30,31,33,35,36,38,39,40,41,43,45, 48,50,52,53,54,55,58,62, 63, 64, 66,67,68,69,71,72,73,74,76,77,78,79,80,82,83,84,85,86, 91,94,96,97,98,99,100,102,103,104,105,106,107,109,111,112,114,115,116,118,121,122, 123,124,125,127,128,130,131,133,136,137,139,140,142,143,145,146,147,148,150,152,153 ,155,156,157,158,160,162,165,170,171,172,173,174,177,178,179,180,182,183,184,185, 186,187,188,190,193,194,195,196,197,198,199,203,204,205,206,207,210,215,217,218,219 ,220,221,222,223,224,225,227,228,229,230,231,232,233,234,235,238,239,240,241,242, 243, 244,245,246,247,248,250,251,253,254,255,256,257,258,262,263,266,267,269,271, 272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,291,294,295 ,296,297,298,299,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,31 8,321,322,323,324,325,326,327,329,330,332,333,334,336,337,340,341,342,345,348,349,3 50,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,369,370,371,372, 374,375,380,382,383,384,385,386,390,392,394,395,396,399,401,404,405,406,408, 407 .

Chapter I. The technique.

1. Physical principles

2. Description of the sonogram

3. Recording and analysing the observed and calculated values.

4. Normal or comparative values.

I. 1. The physical principles.

In 1842, Christian Doppler described the Doppler phenomenon: an emitted wave (i.e. the ultrasound beam) presents a shift in its frequency when encountering a moving target (the red cells). This shift in frequency is decribed by the following formula:

$$df = (2.F.V. \cos a) / c$$

where df = the frequency of Doppler shift;

F = the frequency of the emitted wave in MHz;

V = the velocity of the reflector;

a = the angle between direction of the axis flow and direction of the Doppler beam;

C= the velocity of the wave through the medium. In human tissues, C = 1540 - 1560 m/s at 37 ° C.

In 1880, Pierre and Marie Curie discovered the piezzoelectric properties of quartz crystals: when a force is applied perpendicularly to them, an electric charge appears in them.

These two physical properties are the basis of the Doppler investigation which is very convenient in human clinical practice.

 1. The *transducer* is a device converting energy from one form to another one such as the Doppler phenomenon and the Curie phenomenon. At most soft tissue/soft tissue interfaces in the body, the sound is slightly *reflected (change in the sense of the beam)*.

2. The complete reflection at air interfaces explains the need for a coupling medium such as gel or oil between the ultrasound transducer and the patient. The coupling materials ensures that no air is trapped between the transducer and the skin surface, thereby providing good sound transmission into the patient.

It must be noticed that the gel used should be free of any electrolytes as these can destroy the protecting membrane covering the crystals.

3. Both fat-non-fat interfaces and sharply curved interfaces (such as the walls of vessels) provide the best surfaces for *refraction (change of direction)* to occur.

4*. Attenuation* means the reduction in amplitude of sound beam with distance, and it is dependent of the ultrasonic frequency. In most cases, attenuation is nearly proportional to the frequency and this is one of the limitations of diagnostic ultrasound.

The results will be different according to F. The lower the F, the better the results for haemodynamic assessment; the higher F, the better the results for anatomical analysis.

The frequency range used in diagnostic ultrasounds is a compromise between attenuation losses in tissue and spatial resolution requirements. For most human tissues, the *attenuation coefficient* is equal to 0.5-1dB/cm.1 MHz.

5.According to the Doppler shift equation, the results can also be different because of the *angle's dependency*:

 when "a " is below 15°, differences from real values are less than 4 %; these become 18% if "a " is between 15-30°; and 50% if "a " is above 60°. If the radius of the vessel is known, it is theoretically possible to quantify the blood flow through that vessel:

Blood flow = (mean velocity) x 3.14 x (square root of vessel's radius)

Again, differences from real values can be significant because of the dependency of the square root of the vessel's radius.

In practice, absolute BF measurements are not performed on cerebral vessels owing to obvious anatomical and functional limitations. This can be done by other techniques (near infrared spectroscopy of the brain is a very promising alternative).

I.2. The description of the sonogram .

The transducer converts the acoustic energy coming from the ultrasound beam after its reflection by the red cells, and it allows to trace the sonogram with its **maximum frequency envelope** (see the Figure)**.**

This is the result of a multitude of frequencies from red cells going through different layers within the axis flow. The sonogram also reflects the vasomotion occuring during the cardiac cycle.

Starting from the begin of a cardiac cycle along the zero cross line, the following parameters can be measured throughout a cycle:

1- the peak systolic velocity (SV; VPK on top of the figure);
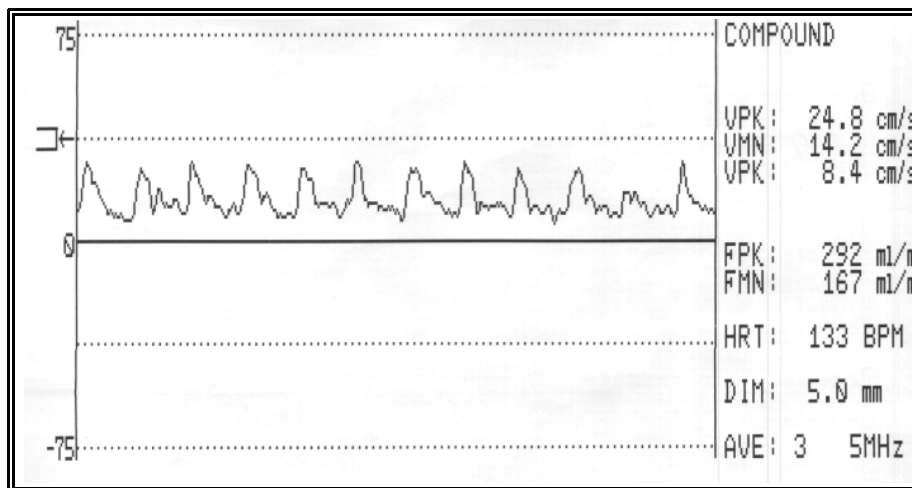
2- the diastolic velocity (DV; VPK on bottom of the figure);
3- the derivated mean velocity (MV; VMN on the figure);
4- the acceleration time to SV (AcT);
5- the deceleration time to DV (DcT);

From these parameters, several indices can be calculated:

6- Indices of impedance to pulsatile flow = resistance indices:
   * RI = (SV-DV)/SV [Pourcelot].
   * PI = (SV-DV)/MV [Gosling].

* S/D ratio.

These indices reflect the vasomotor tone, the blood viscosity and the intraluminal occlusion. The parameters of resistance to flow are given in the Poiseuille's law :

$$R = (8 l n)/r4*3.14$$

where "R " is the resistance to flow, "l " the length of the vessel, "n " the viscosity of blood and "r " the radius of the vessel. **The blood viscosity** (directly proportional) and **the radius of the vessel** (inversely proportional to the fourth power) are, in clinical practice, represented by high haemoglobin levels (> 23 g / dL) and by the vasomotor tone found in the pre-capillary vascular bed.

7- AcT/DcT ratio.

The acceleration time or AcT is depending on wall elasticity of the vessel, blood viscosity and blood pressure gradient. In the figure on the left below, taken from a radial artery, it has a value of 85 msec, with a heart rate of 56 b/min.

The deceleration time or DcT is depending of the blood volume (filling pressure) and of the vessel's resistance (those vessels after the precapillaries arterioles).

In the figure on the right below, it is of 300 msec with a heart rate of 56 b/min. In this case, the Act/Dect ratio is 0.28.
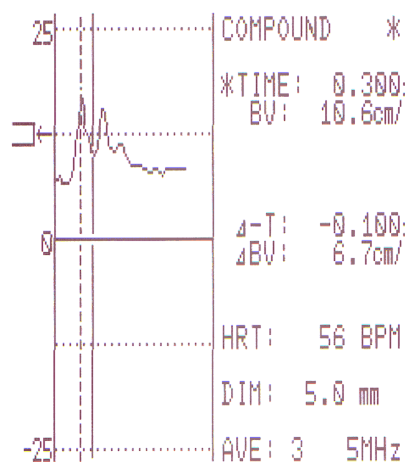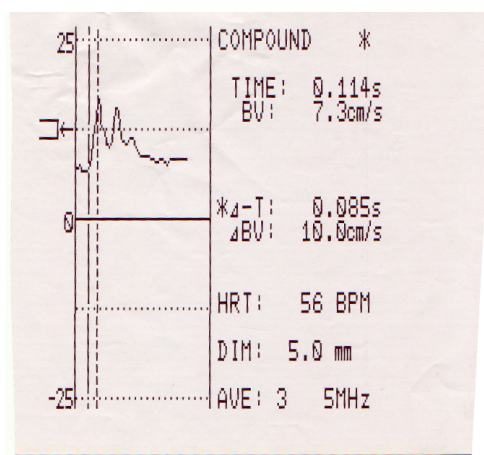
8-The area under the curve (AUC) of the maximum frequency envelope is an index of

cerebral perfusion.

 It is calculated from heart rate and MV by the following equations :

AUC arbitrary units per min = (Hr b/min) x MV

or more precisely: AUC = (Hr b/min) x (1.113 MV + 1.566)

9- Resistance transmission indices.

  They have the purpose to avoid the variations due to cardiovascular factors having their

   origin in the systemic part (heart rate, blood pressure, apCO2):

 -> RTI = (RI studied vessel / RI reference vessel) x 100.

 -> PTI = (PI studied vessel / PI reference vessel)x 100.

   Their normal range is 93 - 107 %.

10 - The intrahemispheric and interhemispheric indices:

 -> the *intra-hemispheric* index is interesting when vasospasm of Middle Cerebral Artery is

      suspected:

   MV in MCA / MV in Internal Carotid Artery (Normal range: 1.5- 2).

   The intra-hemispheric index of perfusion homogeneity also compares the area of perfusion

      of   two arteries:

   MV in MCA / MV in Anterior Cerebral Artery (normal range: 0.7-1.7).

- > the *inter-hemispheric* index of perfusion homogeneity compares one vessel in the left and

      in the right hemisphere:

   MV in MCA one side / MV in MCA other side (normal range: 0.7-1.3).

These indices can be useful to compare the perfusion areas of the ICA, the MCA and theACA

during states such as an occlusive vascular disorder, a ventricular dilatation, a patent ductus

arteriosus, and also when therapeutics procedures are used (drugs, methods of

ventilation, etc ...).

I.3. The record and analysis of observed and calculated

values.

Although from a theoretical point of view several arteries can be analysed, it is commonly reported in studies of either combined or separated measurements on the ACA, the MCA and the ICA. The skull has an effect of acoustic window, and the loss of energy is always inferior to 35 % of the transmitted power. We can distinguish several "*windows* ":

the anterior fontanel, the temporal bone, the orbital area, the foramen magnum, and the neck (see below). The shortest route to a given vessel is not necessarily the best. The uses of two tools can be useful in practice:

i. the use of a plastic lens to focus the energy on a vessel;

ii. the use of an adapter filled with gel and placed at the extremity of the device.

The several windows (W) for placing the probe are:

-F or fontanel for anterior (ACA);

-E or eye for ophtalmic (OA);

-T or temporal for middle (MCA);

-SM or submandibular for carotid (CTA);

-P or posterior for posterior (PCA);

-O or occipital for basilar (BA).

The schematic **presentation of**
the anatomical **approach for**
several cerebral **arteries**
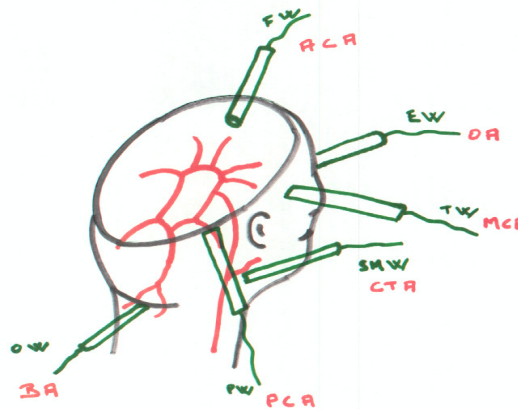
The several windows (W) for placing the probe

Table I.1. The anatomical approach of several arteries: technical aspects.

Vessels	Windows
anterior: ACA	- anterior fontanel, probe directed forward on parasagittal plane; - angle < 10°; - quiet easy to pick up; difficult to differentiate left from right.
Middle: MCA	- parietal bone, just above the plane going from eyes to ears. - very easy to pick up; ankle around 0°.

basilar: BA	- gap between the occipital bone and the atlas; - difficult to pick up.
posterior: PCA	- parietal bone; - difficult to pick up.
vertebral:VA	- through the neck; - very difficult to pick up before one year.
Supratrochlear: STA	- through the closed eyelids ; - difficult to pick up.

The anatomical approach of several arteries: illustrated approaches.

approaching the ACA

approaching the LMCA

There are two types of devices: the continuous and the pulsed types of waves.

In the continuous type of wave, the two transducers, one emitting and one receiving, are located side by side and are recording continuously the signals.They take into account all moving red cells from any layers in the considered vessel. Hence, the instruments using that type of technique are less expensive but also less (about 20 %) precise. In the pulsed type of wave, one gated tranduscer is emitting, and on another time is receiving the signals of sampled depths moving red cells from a selected distance from the transducer (= the sample volume in the considered vessel when combined with a linear array real-time imaging ultrasound device). These instruments are more precise but also more expensive. It is understandable that results from these two types of instruments can be different from each other in their absolute (not necessarily the relative = the ratios) results. In practice however, both are used in the literature.

I.4. The normal or reference values fo the different parameters

This part obviously is not a pleasant one to read. Yet, it does contain numerous numerical informations useful for daily clinical practice and for the elaboration of normative graphs.
(note: CW= continuous wave; PW= pulsed wave).

The different parameters and their normative values are described as follows.

I.4.1 SV cm/sec or peak systolic velocity.

- MCA by CW = 0.96 age in days + 31.2 (SD=6);

      PW = 1.35 age in days + 43.9 (SD=8);

        = 1.7 postconceptional age in weeks - 6.3   (SD =7);

- ACA by CW = 0.75 age in days + 24.4 (SD = 5);

      PW = 1.06 age in days + 34.3 (SD=7);

       = 0.86 SBP - 12.3;

- ICA by PW = 81.7 - 0.75 Hematocrit %;

      = 12.34 + 0.005g of body weight;

I.4.2. DV cm/sec or peak diastolic velocity.

- MCA by CW = 0.09 age in days + 11.4 (SD =0.6);

      PW = 0.126 age in days + 16 (SD = 0.8);

- ACA by CW = 0.15 age in days + 9.9 (SD = 0.9);

      PW = 0.212 age in days + 14 (SD = 1.3);

I.4.3. MV cm/sec or mean velocity.

- MCA by CW = 0.35 age in days + 17.4 (SD = 2.1);

PW = 0.5 age in days + 24.5 (SD = 3);

= 1.1 post conceptional age in weeks - 9.2;

- ACA by CW = 0.43 age in days + 13 (SD = 3);

PW = 0.6 age in days + 18.4 (SD = 3.7);

= 0.0698 age in hours + 6.3;

I.4.4.Correlations between SV,DV,MV.

- SV cm/sec = 3.8 MV - 3.06 DV - 3.66;

- DV cm/sec = 1.24 MV - 0.327 - 1.197;

- MV cm/sec = 0.81 DV + 0.264 SV + 0.97;

I.4.5. Resistance index = SV-DV/SV.

- RI is dependent on several factors:

RI = 0.411 + 0.0192 pCO2 mmHg + 0.00713 hematocrit % + 0.0171 SV cm/sec - 0.0572 MV (r=0.775);

- yet, we can describe a (lower) correlation with a single factor:

RI = 1 - 0.0048 pCO2 mmHg (r=0.55);

RI = 0.00571 age in days + 0.638 (r=0.5);

- **the usual ranges are**: vasodilatation when < 0.5 ; if >0.85 = vasoconstriction.

I.4.6.Pulsatility index = SV-DV/MV.

-This index is less frequently used in studies of cerebral circulation.

The **usual ranges** are:

vasodilatation when < 1.1 ; and when > 2.7 = vasoconstriction.

- PI = 0.0207 age in days + 1.154 (SD = 0.15);

= 0.33 post-conceptional age in weeks - 0.0061 (GA2) - 1.98.

I.4.7 S/D ratio = SV/DV.

Rarely used in cerebral Doppler studies, its **usual ranges are :** vasodilatation if < 2.5; and if

> 3.5 = vasoconstriction;

S/D = 0.031 age in days + 2.5 (SD = 1.9).

I.4.8. Acceleration (AcT) and deceleration (DcT) times.

These are evidently correlated to the heart rate .

The equations are :

-> AcT msec = 0.149 - 0.00054 HR b/m, r = -0.984 ;

-> DcT msec = 0.298 - 0.000107 HR b/m, r = 0.98).

They are also correlated to the gestational age and to the body weight as expressed in the following formula:

AcT msec = 1.3 post-conceptional age in weeks - 12.7

and = 6 Body Weight in g + 18.9.

In practice, it is better o use the ratio: AcT/DcT . This ratio is normally between 0.34 - 0.67 in infants.

Table I.2. The correlation between the heart rate and the acceleration and deceleration times of the sonogram.

heart rate b/m	AcT msec	DcT msec
100	100	200
120	84	166
140	72	143
160	63	125
180	56	111
200	50	100

I.4.9. The area under the curve = AUC.

This parameter, expressed in arbitrary units/min, is a good index of perfusion.

Usual ranges: - in ACA: 400 - 3000.

- in MCA: 450 - 5000.

I.4.10. The criteria for the absence of CBF autoregulation.

Although Chapter II is devoted to cerebrovascular pathophysiology, the equations relating to the loss or absence of CBF autoregulation are given here. If one or more out of the following ratios in a given patient is comprised in these ranges, that means a direct influence of the extracerebral parameters on CBF velocities. These extracerebral parameters are the systolic blood pressure, the pCO2 and the haematocrit:

➔ the ratio [SBP mmHg]/[1.63 Sv cm/sec + 21.3] between 0.54 -1.46.

➔ the ratio [AUC-480]/[22.8 SV cm/sec + 453] between 0.4 - 1.6.

➔ the RI between [0.8-0.0363 pCO2 mmHg] - [1.2-0.0363 pCO2 mmHg].

➔ the MV cm/sec between [18-0.318 haematocrit %] - [29.4 -0.318 haematocrit %].

I.4.11.The indices of perfusion homogeneity.

These indices compare 2 vessels in their observed area under the curve in order to test either the homogeneity of perfusion (which is interesting in suspicion of vessel occlusion or hypoplasia, evoked perfusion during cognitive testing) or the functional integrity of the Willis' circle (see Chapter II).

-> **interhemispheric ratio**: outside the range of 0.7-1.3, there is a significant difference of perfusion between the 2 cerebral hemispheres:

MV in MCA one side / MV in MCA other side.

-> **intrahemispheric ratio:** outside the ranges, there is a significant difference of perfusion between the area of MCA and ACA. This is interesting in cases of ventriculomegaly or occlusive vasculat disorder:

MV in MCA/ MV in ICA (ranges: 1.5-2);

MV in MCA/MV in ACA (ranges: 0.7-1.7);

I.4.12. The resistance transmission indices.

These indices analyse the effects of the intracerebral factors on the impedance to pulsatile flow (and hence taking away factors such as the heart rate, blood pressure, cardiac output, haematocrit and pCO2).

➔ RIT or PIT = (index of actual vessel / index reference vessel) * 100; it should be comprised 93-107. If not, the reason must be intracerebral.

Gathered numbers for the references (see the details at the end of the book) claimed in the chapter I concerning the Technique:
1,11,14,17,25,27,37,38,40,46,47,65,70,75,95,108,117,129,131,135,138,144,150,151,159,176,177,181,202,212,213,215,223b,216,224,237,240,247,248,253,262,289,290,291,302,321,338,343,357,358,365,368,372,373,379,383,384,391,400,401,402.

Chapter II. Pathophysiology of brain ischaemia, hypoxia and hypoglycaemia.

1. Anatomical aspects.

2. Metabolic aspects.

3. Cerebral blood flow autoregulation.

4. Integration of blood flow and metabolic rate.

II.1 Anatomical aspects.

Blood supply to the brain is done by the arteries forming the *circle of Willis*, itself being

supplied in major parts via two systems: the vertebral (VA) and the internal carotid arteries (ICA). The ICA supply mainly the cerebrum. The ICA terminate in the anterior cerebral arteries (ACA) and in the middle cerebral arteries (MCA), and they give rise to the posterior communicating arteries (PCCA). The two ACA connect via the anterior communicating artery (ACCA). The posterior cerebral arteries (PCA) are coming from the basilar arteries (BA) and connect to PCCA. The VA-BA system supplies mainly the brainstem and parts of the cerebrum and spinal cord. The circle of Willis interconnects these two systems.

This vascular structure is important if a compensation of blood supply among the different territories of central nervous system has to be realised, whenever one region of brain is at risk of getting a sufficient blood supply. In the figure (modified from Netter), we see the circle or poligone of Willis and the different arteries emerging out of it.
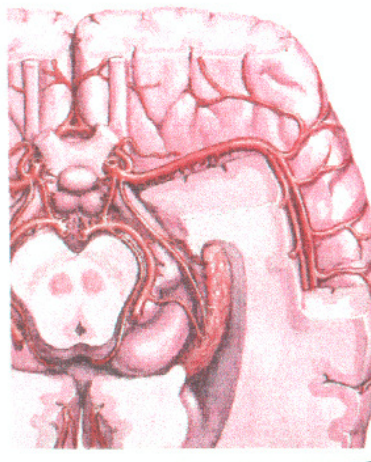
Table II.1. **The main arteries and their area of perfusion in clinical practice (for more details, see precise anatomy as shown in the figures above).**

	Arteries	area of perfusion
Sources: ICA and VA	**ACA**	**medial frontal and parietal lobes; choroid plexus of lateral ventricles**
Sources: ICA and VA	**MCA or sylvian arteries**	**frontal, temporal, parietal and occipital lobes; internal capsule and adjacent structures; midbrain.**
Sources: BA	**PCA**	**temporal and occipital lobes; choroid plexus of 3rd and 4th ventricles.**
	BA	**upper brain stem; midbrain**
	ICA	**choroid plexus of 3rd and 4th ventricles**

As soon as the arteries enter in the cranium, the elastic components of their wall and the vasa vasorum disappear. They become of muscular type. As already said in Chapter I, the impedance to pulsatile flow or resistance index reflect the combination of vasomotor tone, blood viscosity and intraluminal occlusion.

Four different sites of vascular tree within the brain must be considered from a functional point of view:

1° the region before the circle of Willis (ICA+VA+BA);

2° the circle of Willis itself;

3° the part after the circle of Willis and ending at the begin of capillaries;

4° the zone of capillaries of the arterial tree.

These four sites represent respectively 17%, 26 %, 32 % and 25 % of the total vascular resistance to blood flow .

The relaxation ability of the vessel's muscles from baseline tone is different in the various arteries: it is the highest in the ACA and the lowest in the ICA (ACA > MCA > PCA > BA > ICA). The range of relaxation ability from baseline diameter is comprised between 18 - 61%.

The cerebral mass (CM in g) can be calculated from the head circumference (HC in cm) by the following formula according to Dobbing:

$$CM\ g = [(\ HC\ cm\ )3/100] - 1500/HC\ cm$$

In neonates with a normal growth, it represents 14 - 15 % of body weight. This formula is interesting because most values (either metabolic or haemodynamic) are expressed per 100 g of cerebral mass. For instance, the amount of blood in brain (CBV), which is correlated to the CBF,   is comprised between 2.7 and 4.6 ml/100g CM in normal conditions. The neurons and the arterial parameters such as pH, pCO2 and pO2 have their effects (= vasoconstriction or vasodilatation) predominantly on arterioles and pial arteries, and small effects on the large arteries. The growth of vessels follows the one of brain structures: mainly the basal ganglia and the peri-ependymal area before 30 weeks of gestation. After 33 weeks, it will more concern the cerebral hemispheres. The relative proportions of muscles and collagen contents in the wall are changing according to the different parts of the brain, and these changes are markedly seen after 30 weeks.

II.2. Metabolic aspects.

The requirements of glucose (CMRG) and of oxygen (CMRO2) are high in the brain.They are higher for the grey than for the white matter. In normal conditions, there is a coupling between haemodynamic and metabolic aspects. The CBF/CMRO2 ratio is between 14-18.

 The delivery of substrates at cellular level is depending on the CBF and the arterial concentration of the considered metabolite:

$$Cds = CBFx\ aCs.$$

The *extraction rate of metabolite* is actually the ratio between its metabolic rate and its delivery:

Ers = CMRs/ Cds.

Ers can vary according to different factors such as the body temperature, the functional state of the infant (sleep, awake, cognitive action, even anaesthesia) and several pharmacologic agents. To maintain the integrity of cells, it is estimated that forty percent of O2 and glucose extracted by the brain are used to maintain that integrity, and fifteen percent are abolutely necessary to the immediate survival of the cells. The other sixty percent are devoted to function outside for maintaining the integrity, for synthesis and for growth.

From the Table II.2, it can be seen that the CMRO2 and CMRG are around three times higher in grey matter (GM) than in white matter (WM). The molar ratio [glucose/oxygen] is around 1.4, meaning that a significant amount of glucose is anyway used for the anaerobic glycolysis.

Table II.2. Cerebral metabolic rates for glucose (CMRG mg/100g/min) and for O2 (CMRO2 ml/100g/min)

	global tissue	grey matter	white matter
CMRO2	3.2	2.4	0.8
CMRG	5	3.7	1.3
Molar ratio G/O2	1.38	1.1	1.17

As cerebral tissue is represented for about 80 % by WM, the anaerobic use of glucose is mainly encountered in WM. The brain tissue has a relative ability to modulate its functional state from above the integrity zone up to all possible functions, according to the haemodynamic and metabolic opportunities.

The interesting applicatio of the Doppler technique investigations on the arterial brain circulation is precisely in the assessment of these haemodynamic events. When the brain

has to face ischaemia, hypoxia, hypoglycaemia or pharmacologic factors, adaptative mechanisms such as changes in CBF, CDO2 or CMRO2 are accompanied by changes in CBFV, resistance indices or AUC.

II.3. The Cerebral blood flow autoregulation.

CBF autoregulation is a general concept meaning that the cerebral functions remain constant despite changes of parameters such as arterial pCO_2 or pO_2, blood pressure, arterial content in oxygen. The plateau phase of CBF is the reservoir zone of CBF autoregulation against possible changes of parameters outside the brain. From studies both in animals and humans, it is smaller in a patient with a lower gestational age, and even disappear in presence of respiratory distress, circulatory failure, hypoglycaemia or anaesthesia. The correlation becomes linear between these parameters and the CBF. The cerebral vessels of the healthy newborn infants, whether premature or mature, respond to physiological stimuli in the same manner, and this shortly after birth, although cerebral reactivity tends to increase with gestational age.

The CBFV and derivated indices can be influenced by changes in the values of haematocrit, blood pressure, cardiac output, pCO_2 and pO_2, the glucose and oxygen contents in arterial blood, and to the effects of several therapeutic agents.

Table II.3. Relative changes of CBFV (d CBFV from baseline) by several extracerebral parameters.

Parameters	DCBFV : in % or cm/sec
cardiac output (1)	1 cm SV / 8 ml
mean blood pressure (2)	1.5 cm SV/mmHg or 0.15 cm MV/mmHg
pCO2 (3)	3-4 % / mmHg
haematocrit (4)	0.35 cm MV/1%

(1): outside the range of 190-440 ml/kg/min;

 (2): outside the range of 30-40 mmHg;

(3): outside the range of 38-42 mmHg;

(4): outside the range of 30-70.

These effects are mainly observed in pial arterioles, and, to a lesser extent, in large arteries. The cardiac output (CO) and blood pressure (BP) have similar changes upon CBFV, and hence one can use either indifferently. Moreover, either abrupt changes in CO or BP are followed by ten times higher changes in SV (this is mainly relevant to the rupture of vessels) than MV or area under the curve (this is more relevant to the perfusion).

There are three subsystems for CBF autoregulation control:

1°= one for the independency against changes in BP;

2°= one for the independency against arterial changes in pCO_2;

3°= one for the independency against changes in arterial oxygen content.

When insufficient amounts of glucose or oxygen are delivered to the brain, CBF independency for these parameters disappears in that order.

CBF or CBFV will decrease with a lower pCO_2, cardiac output, blood pressure; with a higher haematocrit, pH, arterial contents of oxygen and glucose. The reverse changes will increase CBF or CBFV.

The loss or the absence of CBF autoregulation is found in the following clinical conditions:

➔ an arterial glucose level < 24 mg/dL.

➔ a respiratory distress syndrome.

➔ an intracranial infection.

➔ an arterial glucose level < 24 mg/dL.

➔ a respiratory distress syndrome.

➔ an intracranial infection.

➔ a head trauma.

➔ a cerebral infarction.

➔ a blood hypertension or hypotension.

The precise criteria to make the diagnosis of CBF autoregulation are given in the section I.4.9. In practice, CBF autoregulation is absent if any changes of parameters given in the Table II.3 is followed by the described changes in CBFV.

II.4. Integration of blood flow and metabolic rates in pathophysiology.

In normal conditions:

CBF, Cds, CMRs, Ers, arterial content of oxygen and glucose, cerebral blood volume (CBV) are correlated between them.

These correlations are:

* CBF/ CMRO2 ratio ml/100g/min = 14-18.

* CBF in ml/100g/min = 23 - 0.132 Glycaemia in mg/dL.

* CMRO2 in ml/100g/min = 0.07 CBF in ml/100g/min -0.55.

* CMRG in mg/100g/min = 0.75 CBF in ml/100g/min - 0.39.

* CMRG/CMRO2 ratio in mmoles = 1.4.

* ER O2 = 0.0074 CBF in ml/100g/min + 0.019.

* ER O2/ ER G = 3.5 - 4.

* CBV in ml/100g = 0.062 CBF in ml/100g/min + 2.1.

* d CBV / d CBF = 0.9

Owing to modifications in CDO2 or CDG throughout the tissues, the brain is relatively able to adapt its activities above those of maintaining integrity of cells, for all areas or for regional parts of the brain tissue (= the normal intra-tissular functional adaptation mechanisms). So does also the body to protect the brain, the myocardium, the surrenal glands, at the expense of the skin, muscles, digestive tract, kidneys.

Table II.4. Cerebral metabolic rates for glucose and oxygen : integrity and all function for cells.

	In the white matter	In the grey matter	In global tissue
CMRO2 in ml/100g/min: integrity	0.3	1	1.3
CMRO2 : all functions	0.8	2.4	3.2
CMRG in ml/100g/min: integrity	0.7	2.1	2.8
CMRG : all functions	1.3	3.7	5

The activities for conservation of cell's integrity are:

 i. to maintain the normal cellular composition of electrolytes, water, ATP, and osmolality;

ii.to maintain the membrane's potentials;

iii.to elaborate the synthesis of molecules having to be replaced.

In conditions where CBF autoregulation is absent, CBF will be variable according to variabilities of extracerebral parameters, mainly the blood pressure. In healthy adults, CBF is around respectively 40-50, and it is 15 ml/100g/min in healthy premature neonates. In sick premature neonates, CBF is usually comprised between 10-12 ml/100g/min, but can be found below 10ml/100g/min .

Table II.5. According to a variable cerebral blood flow: the calculated arterial values for glucose in mg/dL and for oxygen in ml/dL in order to maintain the activities of cells in brain above the required demands for integrity and the corresponding proportion of

that for all brain functions (% W).

CBF ml/100g/min	glucose in mg/dL	Oxygen in ml/dL	CBV in ml/100g
5	137 (30)	30 (2)	2.41
10	99 (40)	28 (5)	2.72
15	53 (7)	26 (16)	3.03
20	34 (12)	24 (25)	3.34
30	31 (22)	22 (50)	3.96
40	25 (32)	18 (75)	4.58
50	21 (42)	15 (90)	5.82

CBF or cerebral blood flow in ml/100g/min; CBV or cerebral blood volume in ml/100g.

 If the number between brackets is < 10, the reserve of the corresponding circulating metabolite is nearly absent.

When CBF is decreases, CBV, CMRO2, CMRG also decrease. Arterial contents in glucose and oxygen need to be increased. CBF values below 15 require level of glucose above 50 mg/dL, and of oxygen above 25 ml/dL. This means in practice an haemoglobin level, if well saturated, above 15 g/dL. For values of CBF below 15 ml/100g/min, CDO2 and CMRO2 are very near the integrity zone. The percentage allowed for the other activities is small or nearly absent (16 % at 15; solely 5 % at 10; and 2 % at 5 ml CBF/100g/min). On the glucose side, this situation can partially be compensated by relatively high CDG and CMRG, although it is meaning that larger quantities of glucose are used anaerobically, probably to provide some ATP. Just above the integrity zone, there is a sort of boundary zone where the brain will induce adaptive mechanisms in order to re-establish either the delivery of blood volume or metabolites, or to maintain some functions , yet having to suspend several cellular activities. This is done at the expense of either other tissues (the intra-body blood flow redistribution) or either of different parts within the brain (the intra-tissular redistribution). For instance, the protected areas are the cortex, the brainstem and the basal ganglia, while the white matter

area is particularly at risk of insufficient deliveries in glucose and O2.

The Doppler technique can help to investigate these phases. Indeed, and without going into details of cellular events after insufficient CDG and/or CDO2, vasoconstriction can be observed within minutes during a period going up to 45 - 60 minutes. Vasodilatation will follow for a period of several hours (up to 48 hours). These facts can be reflected by abnormalities in the resistance indices, as described in cerebral oedema or in intrauterine growth retardation (see below).

The blood-brain-barrier components and the relationships between cells and vessels (microcirculation) are shown in the figure (modified from Chusid).
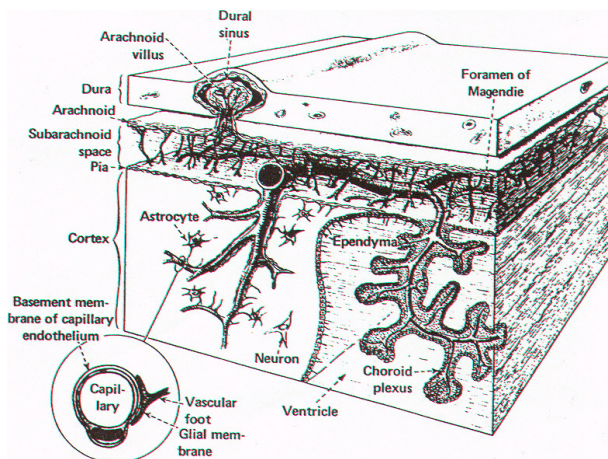
According to developmental histology and biochemistry of the brain, the cellular alliance between the neurons and glial cells is particularly relevant in perinatal and neonatal periods**.**

The neuronal migration is ending at a postnatal age of 4 months in the brain and of 12 months in the cerebellum.

At cellular levels, it is the unit " one neuron + 5 to 7 glial cells and the related blood-brain-barrier " that needs to be considered in Fetal and Neonatal Medicine. That unit includes two cell types with different demands for O2 and glucose. The glial cells are providing metabolites to the neuron for energy, synthesis and repair (= glucose, intermediary metabolites of tricarboxylic cycle, aminoacids), clearing the perineuronal milieu of toxic molecules such as free radicals, clearing or buffering the excess in excitatory aminoacids, nitric oxide, interleukins, potassium, calcium and iron.

As those units are still being present in the white matter, there is a real danger for these cells'survival as reflected by the location of brain injuries in the sick preterm or term neonates. Indeed, as most of the fibers are passing through the periventricular area (particularly in the internal capsule), it is understandable why the so called ischaemic brain injuries are frequently located in that area.

Table II.6. The cellular events (the cascades) after brain hypoxia, ischaemia, hypoglycaemia.

Events	Results
- decrease of CDO2,CDG; - increase of CDCO2,CDH+**;**	- absence of CBF autoregulation within minutes.
- large release of excitatory aminoacids, cytokines, calcium, hydrogen, potassium, free radicals, nitric oxide, thromboxane, endothelin; - decrease of ATP**;** **-** increase in numbers and sensitivity of receptors to EAA.	**-** blood brain barrier: leakage for small molecules (15 min) and after for large molecules (120 min); - vasoconstriction (-> 60 min); vasodilation (-> 48 hrs); blood flow redistribution: increase in cortex, decrease in WM. - injuries in dendrites and axons (10 min), in cellular bodies (30 min); pericapillaries cells clustering and edema; further : proteolysis of cytoskeleton, mitochondrial damage **,**DNA fragmentation, venous congestion, macrophages digestion of cells.
- release of dopamine, adenosine, endorphins; - increase of antioxydants defenses, of neurotrophic synthesis, of astrocytes intervention, of synthesis of stress protein; - first decrease and further increase in synthesis of several proteins.	Regeneration or repair**:** Production of healing factors with an optimal level at about 10 days after insult.

Gathered numbers of references (see details at the end of the book) in chapter II concerning the pathophysiology:
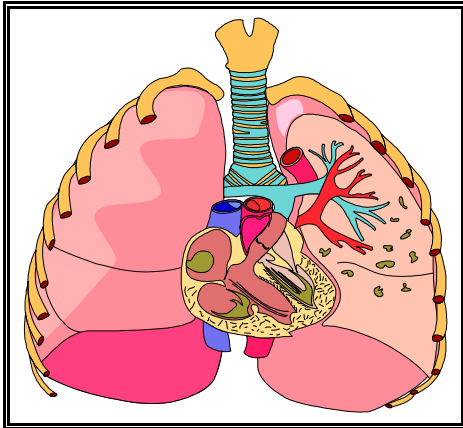
23,24,48,57,63,92,102,114,136,143,146,152,156,157,160,161b,162,166,187,190,199,205,
207,221,255,255b,263,266,275,280,301,303,319,320,325,336,337,349,350b,355,370,385,390
,404,406.

Chapter III. Cerebral haemodynamics during acute and prolonged respiratory distress.

1. The neonatal respiratory distress syndrome (RDS).

2. The chronic lung disease (CLD).

3. Discussion.

III.1. The acute respiratory distress syndrome.

Among sick newborn infants, the respiratory distress syndrome or RDS is a frequent situation, mainly in the very low birth weight babies. These infants frequently need to receive a support to improve their respiratory and circulatory states such as oxygen, mechanical ventilation, surfactant, steroids, inotropic drugs, colloids and transfusion. They also may have to receive other drugs for infection, sedation, pain, convulsions, etc... Owing to the incidence of brain acquired injuries and their relationships with the abnormalities of haemodynamic factors, the RDS is at the same time an interesting and a difficult medical situation for the Doppler investigation.

We may consider that technique as a stethoscope for the brain.

The CBF autoregulation is fragile or even absent in the infants with RDS. CBF and CBFV may be directly dependent on changes of blood pressure or cardiac output and, to a lesser extent, on changes of pCO2 and blood oxygen content.

From minute to minute monitoring of simple parameters such as blood pressure, heart rate and transcutaneous pO2, one can see that variations of heart rate precede those of TcpO2 within about 60 sec, and these lasts also precede those of BP within 90 sec.

As already mentioned, CBF is correlated to blood pressure and blood gases:

- CBF ml/100g/min = 1.25 SBP mmHg - 36.

- CBF   = 269.212 + 1.084 SBP - 0.336 apCO2 mmHg - 0.0072 apO2 mmHg -

38.16 pH.

We had the opportunity to investigate prospectively 49 sick premature infants with a RDS during their first week of life, when they were mechanically ventilated. They were born at mean gestational age of 28 weeks (range: 25-32) and with a mean birthweight of 960g (range : 600-1560).

The extracerebral parameters (= cardiac output measured by real-time ultrasounds at the aortic valve, the invasive blood pressure, the arterial pH and blood gases, haematocrit and haemoglobin, heart rate) and the intracerebral parameters (the blood flow velocities on sample volumes from ACA) were analysed. The babies were looked in three body's positions, always in the same sequence: 1° baseline = horizontal; 2° upper position = head at + 30 degrees; 3° down position = head at - 30 degrees. The total number of studied episodes was 441. Measurements were made as soon as possible after birth, and then at 24, 48 and 72 hours of age The combined Doppler (5 MHZ pulsed wave) and real-time ultrasounds (7.5 MHZ) technique was used (Diasonics CV 400, Sonotron). We observed the following results.

>Cerebral blood autoregulation was found to be absent.

Cerebral haemodynamics (CBV , RI and AUC on ACA and MCA) were statistically correlated to extracerebral parameters, signing their dependency to the cardiac output, the blood pressure, haematocrit and pCO_2:

- cardiac output ml/kg/min = 7.6 SV cm/sec + 151 (r=0.98);

$\qquad$ = (AUC - 482) / 3.13 (r=0.73);

$\qquad$ = 57 MV cm/sec - 178 (r=0.672);

- RI = 1.37 + 0.0015 SV cm/sec - 0.00648 pCO_2 mmHg - 0.005 haematocrit % - 0.0087 MV cm/sec (r=0.726).

$\qquad$ = 1 - 0.0048 pCO_2 mmHg (r=0.597);

- MV cm/sec = 23.64 - 0.318 haematocrit % (r=0.61)

- SV cm/sec = 0.86 SBP mmHg - 12.3 (r=0.5).

The relative changes in SV and MV by the cardiac output or blood pressure were similar when these were compared to each other. This means that monitoring blood pressure (more

easily obtained than the cardiac output) gives precise informations on the cerebral haemodynamic changes.

In healthy neonates, no correlation was found between the extracerebral and intracerebral parameters (signing their independency), nor between the extracerebral parameters.

In sick neonates, however, the cardiac output (CO), the blood pressure (SBP) and the heart rate (HR) were correlated to each other:

- CO ml/kg/min = 12.3 SBP + 76.62 (r=0.641);

- CO ml/kg/min = 2.96 HR b/m -121.5 (r=0.541).

In sick neonates, changes of blood pressure or cardiac output were followed by ten times higher changes of SV (--> direct influence on the vessel wall : this is more relevant to haemorrhagic lesions) than of MV or AUC (--> direct influence on tissue perfusion or flow : this is more relevant to ischaemic lesions).

-->Haemodynamic variability was nearly absent.

Neurovegetative reactivity was assessed by looking at the effects of sequential changes of the body's position on the extracerebral and intracerebral parameters. This was done when the infant was awake and was stable as far as respiratory and circulatory aspects were concerned.

Table III.1. Haemodynamic reactivity in premature neonates with RDS: effects of changes of body position (n=441; Mean +- SD).

Body position	CO ml/kg/min	RI
head up 45 °	280 +- 170	0.73 +- .29
head at 0° (=baseline)	265 +- 125	0.76 +- .24
head down 45°	315 +- 165	0.65 +- 0.25

Overall, the differences between the three positions were not statistically significant, even if the most marked tendency concerned the RI, mainly a tendency to vasodilate in head down position.

-->The influence of surfactant therapy was evident and variable.

The effects of surfactant therapy on haemodynamics in newborn infants with RDS reported in the literature are variable. That therapy has no fully predictable effects on cerebral haemodynamics . In the study population, although the infants were mechanically ventilated and were optimilized for blood pressure, pH and blood gases **before** surfactant therapy was started, this therapy induced significant changes on both extracerebral and intracerebral haemodynamics. The observations , expressed in changes from baseline, were:

- always an increase of 15-27 % of systolic blood pressure;
- always an increase of 1-37 % of mean blood pressure;
- in Systolic Peak Velocity in brain , an usually but not always increase (as the variations went from - 56 up + 96 %);
- in Mean velocity, usually an increase, but here also the variations went from - 65 up + 159 %;
- in Area Under Curve, usually an increase, but again the variations went from - 59 upt + 143 %;
- in RI: usually a decrease, but variations went from - 24 up + 14%;
- the AcT and DcT didn't statistically change;
- the heart rate didn't statistically change.

These changes were abruptly observed within 5-10 minutes after intra-tracheal surfactant instillation. It must be noticed that the most striking changes were those concerning the SV, MV and the AUC.

III.2. The chronic lung disease or the prolonged oxygen dependency after RDS.

About 25 % of infants who have severe RDS remain dependent of oxygen therapy for several weeks ("chronic lung disease or bronchopulmonary dysplasia ").
We had the possibility to follow prospectively 8 infants with CLD. They were born with a median gestational age of 29 weeks (range 25-30), and a median birthweight of 1070 g (range 615-1220). They were examined at a median age of 110 days (range 59-233) or at 39 weeks postconceptional age (range 37-64). The number of episodes studied was 72.

-->CBF autoregulation was present.

There were none correlation between CBFV, AUC, RI on one hand, and the cardiac output, blood pressure, arterial pCO2 and haematocrit on the other hand (signing the independency from each other).
Moreover, cardiac output, heart rate and blood pressure were not correlated .

-->Neurovegetative haemodynamic variability was present.

When they were tested on the three different body's position, intrinsic reactivity induced significant changes:
- increase in cardiac output,

> in AUC

> and in diastolic velocity in head down position.
- RI remained stable however.

Table III.2. Haemodynamic reactivity in infants born prematurely with a RDS and

having a prolonged oxygen therapy.

Body position	Cardiac output Ml/kg/min	AUC/min	RI	DV cm/sec
head up + 45°	346 +/- 58 **	2,416 +/- 1,120	0.6 +/- 0.29	10.5 +/- 8
head at 0°	309 +/- 119	2,341 +/- 600	0.56 +/- 0.85	9.5 +/- 3.5
Head down 45°	403 +/- 38 **	3,232 +/- 1,561 **	0.58 +/- 0.09	14 +/- 8.5 *

* means p < 0.01, ** means p < 0.001 in differences from baseline (Student's t-test, n=72; mean +/- SD). DV = diastolic velocity.

III.3 Discussion on the interrelations between the brain, the heart and the lungs

It is interesting to make some comments on the clinical conditions and to see what is happening in the brain, the lung tree and the heart: from the physiology knowledge, see what is going on in our population and what is reported in the literature.

Theoretically (physiology knwoledge).

The *neurological pathways* are mainly represented by the Xth- and the IXth- pairs of nerves. The *hormonal languages* are the signals coming from the chemoreceptors influenced blood substrates concentration (H+, CO_2, O_2, glucose) . The signals from the baroreceptors are influenced by haemodynamic parameters (systolic and/or diastolic blood pressure, heart rate, blood flow, blood flow velocity).

There is a communication between the brain, the heart and the respiratory tree through these two systems.

➔ The main concerned area in the brain is the anterior hypothalamus.

➔ Outside the brain, the frequent reasons for a decrease of CO or BP are a hypovolhaemia, a vagal stimulus, a venous dilatation, an obstruction of the large veins, a patent ductus arteriosus or a cardiac impairement. The chemoreceptors and baroreceptors are located in the aorta and the carotids.

➔ However, the chemoreceptors in brain are more rapidely sensitive to changes in pCO_2 and H^+.

➔ The face, and especially the nose of the infant are very sensitive, to pain and changes in temperature.

➔ Notes:

-delta = any changes of parameters;

- V = volume;

- BP = blood pressure;

- CO = cardiac output;

-AV = alveolar ventilation;

- VCS = vasoconstrictor (neuronal) center;

-VDS = vasodilator (neuronal) center;

- IS = inspiratory (neuronal) center;

- ES = expiratory (neuronal) center;

- RR = respiratory rate / min;

- HR = heart rate / min;

- CSF = cerebrospinal fluid;

- mod = modulation possibilities by: endorphins, analgesia / anaesthesia, rapidity or duration   of changes of a given parameter; by a lung state (emphysema, atelectasis, pneumonia, irritants); by delta of CBF; by activity of IXth or Xth nerves.)

Table III.3. Afferent and efferents pathways of actions and reactions between the heart, the lungs and the CNS.

Structures	Afferent	Efferent	Results
Cortex	Receptors:delta BP, CO, temperature (skin,viscera) pO2,pCO2,H+ Pain, tactile	Via hypothalamus with modulation	Variable; activation of hypothalamus-> VCS/VDS; delta of blood flow distribution; release of endorphins.
Hypothalamus	Same as cortex + delta V of CSF	Via cortex and trunk with modulation	Variable; activation of cortex and trunk-> VCS/VDS. Delta of BFlow
Veins	Trunk: VCS/VDS	Sympathetic, X, IX	Delta impedance to flow and BFflow
Arteries	Trunk: VCS/VDS	Sympathetic,X,IX	Delta impedance to flow and BFlow
Heart	Trunk and cortex, X and IX nerves	Conductive tissue and heart ventricles	Delta HR and stroke volume
Lungs	J receptors and irritant receptors	Trunk: IS/ES, X and IX nerves	Delta RR,AV, delta BP, CO, pO2,pCO, pH
CNS:trunk:VCS	Hypothalamus	Sympathetic,X,IX	Delta vessel resistance delta BP, CO, pO2,pCO, pH
CNS:trunk:VDS	Hypothalamus	Sympathetic,X,IX	Delta vessel resistance delta BP, CO, pO2,pCO, pH
CNS:trunk:IS	Lungs	Sympathetic,X,IX	Delta RR and AV
CNS:trunk:ES	Lungs	Sympathetic,X,IX	Delta RR and AV
Hypothalamus	Baroreceptors, chemoreceptors, cortex, V brain ventricles	Sympathetic,X,IX	Delta BP, CO, pO2,pCO, pH

In practice

1- All these situations eliciting the receptors are very important and are frequently

encountered in neonatal intensive care: during pharyngeal or tracheal aspiration, or during surfactant instillation, or endotracheal intubation.

2- Let us also consider *the importance of the cerebral mass* and the circulatory characteristics in the considered population of infants.

Table III.4. Comparison of the cerebral mass/body weight ratio (CM/BW in %), the cardiac index (L/M2) and the cerebral blood flow/cardiac output ratio (CBF/CO in %) in the four groups of infants.

Groups	CM/BW ratio in %	cardiac index L / m2 body surface area	CBF/CO in %	CBF ml/100g/min
1 = RDS (n=441)	10.2 +- 0.8	2235 +- 1174	11.2 +- 5.95	5.5 +- 3
2 = CLD (n=72)	14 +- 6	2848 +- 285	22.6 +- 6	16 +- 4
3 = Growth retarded (n=124)	14.6 +- 11	2891 +- 1611	21.4 +- 15.6	15 +- 10
4 = Controls (n=132)	13.5 +- 0.9	3296 +- 1570	16.3 +- 7.7	13 +- 6
statistical comparison bewteen groups	CM/BW ratio in %	cardiac index L / m2 body surface area	CBF/CO in %	CBF ml/100g/min
1 and 2	< 0.01	< 0.05	< 0.01	< 0.001
1 and 3	< 0.05	< 0.05	< 0.01	< 0.05
1 and 4	< 0.001	< 0.05	< 0.05	< 0.01
2 and 3	Ns	Ns	< 0.05	Ns
2 and 4	Ns	< 0.05	< 0.05	Ns
3 and 4	Ns	Ns	< 0.05	ns

As the gestational ages were not equivalent between the three groups, we calculated the correlation of the ratio CBF/CO with gestational age and the CM/BW ratio.

The correlations were:

> (CBF / CO)*100 = 1.05 GA weeks - 18.3 (Sy = 5.2; r = 0.99) where CBF is expressed in ml/100g/min and CO in ml/kg/min.

Example: at 28 weeks, CBF/CO = 11.2 +- 5.2; and at 40 weeks, it is 23.7 +- 5.2.

> (CBF / CO) * 100 = 243 (CM / BW) - 14 (Sy = 5.2 ; r = 0.92) where Cerebral Mass and Body Weight are expressed in g.

Examples :

- Head circumference = 25 cm, and CM = 96 g; and BW = 700 g,

  then CBF/CO = 19 +- 5.2;

- HC = 35 cm, and CM = 386 g; and BW = 3000g, then CBF/CO = 17 +- 5.2.

The ratio cerebral blood flow/ cardiac output increases with gestational age (and hence with the absolute cerebral mass and body weight as these increase with GA), and that ratio remains relatively stable with respect to the ratio mass of brain/ body weight (which can be different among babies, for instance in growth retarded newborns).

This means that the significant differences observed in CBF/CO ratios among the different groups aren't explained by the also significant differences in CM/BW ratios among them nor by the gestational age.

The following aspects are relevant:

-i. those infants with the clinical conditions eliciting a brain privilege for growth (those growth retarded already in utero and those growth retarded extra-utero such as the ones with a chronic lung disease) seem to maintain a better CBF/CO ratio;

-ii. those with acute disease haven't neither the ideal circulation nor the ideal metabolic conditions to satisfy the complete brain growth;

- iii. and finally, those born after a normal fetal growth and living with normal conditons in respiration, circulation and nutrition can elicit an equivalent privilege for all tissues, not only for the brain.

It is precisely in the sick premature infants that the following conditions are found:

➔ a precarious state of respiration, circulation;

➔ a present but fragile neurovegetative support;

➔ an absence of cerebral blood flow autoregulation (and hence a cerebral blood flow dependent of blood pressure, blood gases, pH, oxygen and glucose arterial contents);

➔ a low cerebral blood flow, and a nearly complete interdependency of blood pressure, cardiac output and heart rate.

➔ These infants are, at a purely figurative level, treated or assisted while they have to produce tremendous efforts " to swim with the mouth just above the level of water ". In the group of term or near term infants who experienced a fetal growth restriction, it must be mentioned that they have a present but fragile cerebral blood flow autoregulation, a present but fragile neurovegetative support, and that they seem to have privileged the brain.

 Gathered numbers of references (see details at the end) for chapter III: The respiratory difficulties:

 26,30,35,38,45,48,49,51,68,77,81,86,104,107,136, 141,144,153,169,174,178,180,196,198,206,226,227,235,238,241,242,244,246,260,261,265, 272,283,290,295,296,326,331,332

Chapter IV. The effects of several drugs on the cerebral blood flow velocities.

1. **Drugs inducing a decrease of cerebral vascular resistance.**
2. **Drugs inducing an increase of cerebral vascular resistance.**
3. **The effects of drugs improving the blood pressure.**
4. **The effects of general anaesthesia.**
5. **Discussion.**

It seems useful to devote a special place to the effects of the drugs on the

resistance of cerebral circulation.

Clearly, these effects are concerning only the vasomotor tone (in most of cases) or the blood viscosity (in rare situation).The intraluminal occlusion aspect, yet possibly encountered (= " the occlusive vascular disorder ") is usually not concerned by the medical therapies.

Their final action can be located either in the smooth muscles of the vessels, or in the myocardium, or in the cellular metabolic rate, or in the receptors of brain cells membranes. One has also to take into account that the drugs can have different effects depending if they are given isolated or in combination, and depending also of the pathophysiology actually present in the patient.

 Many therapies have been analysed regarding their effects on cerebral haemodynamics: atropine, bicarbonate, acetazolamide, anti-prostaglandins, inotropics, dexamethasone, surfactants, barbiturates, fentanyl, morphine, nimodipine, nifedipine, tolazoline, anaesthetics, oxygen, mechanical ventilation, infusions of albumin, of red cells, blood exchange, midazolam, Vit E, Vit C, xhantines, naloxone, excitatory aminoacids blockers, curare, etc...[see the gathered references]. *The medical and surgical problems of the patent ductus arteriosus will be approached in a further chapter.*

IV.1. The drugs decreasing the cerebral vascular resistance.

By decreasing the impedance to pulsatile flow, several drugs can increase the cerebral blood flow:

- ➔ inhaled anaesthetics = halothane, enflurane, isoflurane, nitrous oxyde;
- ➔ ketamine;
- ➔ nitrotroprusside (sodium);
- ➔ naloxone;
- ➔ lidocaïne;
- ➔ nitroglycerine;
- ➔ succinylcholine, d-tubocurarine, pancuronium;

➔ acetazolamide if there is a concomitant high pCO2;

➔ nimodipine and nifedipine.

Inhalation anaesthetics, ketamine and succinylcholine induce also an increase of intracranial pressure.

Isoflurane can be considered as having protective effects.

Let us remind that other parameters such as acidosis, hypercapnia, hypoxia do also increase the cerebral blood flow.

IV.2 The drugs increasing the cerebral vascular resistance.

By increasing the impedance to pulsatile flow, these drugs can decrease the cerebral blood flow. We may list the following ones:

➔ althesin;

➔ barbiturates;

➔ etomidate;

➔ midazolam;

➔ propofol;

➔ fentanyl and sulfentanil;

➔ droperidol;

➔ indomethacine and ibuprofene (more marked with high mean airway pressure);

➔ theophylline and cafeine;

Blood alkalosis, hypocapnia, hyperoxia and interleukins also decrease the cerebral blood flow. Barbiturates, althesin and etomidate can increase the cerebral perfusion pressure and decrease the intracranial pressure.

IV.3.The therapies improving the blood pressure.

Hypotension is the most important and frequent haemodynamic situation encountered in neonatal intensive car. However, it is not well defined in the literature, and we use the reference values of the mean blood pressure from Raju and Bada . We use the 95% CI of the arterial mean blood pressure according to gestational age, trying to avoid fluctuations of its baseline greater than 15% per minute and, in case of having to treat hypotension, trying to get its normalization within (ideally) 2 to (lastly) 6 hrs. The mathematical correlation is:

mean BP torr = 0.78 GA weeks + 9 [sd = 2.13, r=0.959].

Table IV.1. 95 % CI of arterial mean BP according to gestational age in weeks

Gestational age	MBP
25 weeks	24-32
27	26-34
29	28-36
31	29-37
34	32-40
37	34-42
40	36-44
43	39-47
MBP torr equation	= 0.78 GA + 9 (SD 2.13)

Hypotension is frequently encountered during the acute respiratory distress syndrome in the premature infant. In order to improve the cerebral perfusion, usually in the low ranges in this type of situation, theses neonates have to be treated by colloïds infusion and inotropic drugs (dopamine, dobutamine, isoprenaline, levorenine).

We had the opportunity to make a prospective study in 14 babies born at 31 +- 2.8 weeks, with a birthweight of 1610 +- g, a body length of 43 +- cm and a head circumference of 30.4 +- 1.5 cm. They had a RDS and were mechanically ventilated. They had an arterial hypotension within a median age of life of 2.25 h (ranges: 1.4 - 8.6 h). They were treated by first albumin infusion (1 g/kg in one hour), secondly by inotropic drugs (dopamine 5 -> 10 microg/kg/min; dobutamine was added if dopamine wasn't sufficient: 10 microg/kg/min). A normal blood pressure was obtained within 2.75 h (median period). The analysis of the cerebral and extracerebral parameters was done during 5 +- 1.8 hrs, this period did cover the pre-during-just after treatments for hypotensive periods. The left middle cerebral artery was continuously monitored, and blood pressure was continuously monitored via a radial catheter. We were able to make the distinction between the effects observed during the colloïds infusion and those during the infusion of inotropic drugs.

The differences observed in systolic, diastolic and mean blood pressures (= increases), in cerebral blood mean velocities (= increases), in acceleration times (= increases), in deceleration times (= increases for albumin, decreases for inotropic drugs), in resistance index (decreases) were statistically significant. The colloïd infusion had more marked influences than the inotropic drugs. Overall, the better systemic perfusion and the better cardiac performances were accompanied by a better cerebral perfusion. The tremendous effects observed suggest in clinical practice a not too rapid correction of blood pressure, in order to avoid high and rapid fluctuations in cerebral haemodynamics. One could advise to make this type of correction in a period comprised between 2 - 4 hours.

Table IV.2. Observed haemodynamic differences during colloïds and inotropic drugs infusion to treat early hypotension during RDS (median values in % from baseline).

Parameters	colloïds infusion (n cycles = 675)	Inotropic drugs infusion (n cycles = 1012)
Blood pressure: Systolic	+ 21	+ 11
Diastolic	+ 30	+ 28
Mean	+ 27	+ 17
CBV: mean	+ 70	+ 46
RI	- 8	- 15
Ac time	+ 37	+ 27
Dc time	+ 14	- 13

Baselines values: SBP torr = 45 +- 10; DBP torr = 24 +- 3; MBP torr = 34 +- 9; MV cm/sec = 6.5 +- 3.4; RI = 0.93 +- 0.08; Ac time msec = 69 +- 19 ; Dc time msec = 145 +- 53.

IV.5 The effect of general anaesthesia

When talking about anaesthesia in infants, one firstly has to consider the general clinical conditions before the anaesthesia and the indication of surgery, and then the type of drugs used for anaesthesia.

From our experience, we can provide data for infants stable and being operated for inguinal hernia, pyloric stenosis or extraperitoneal abdominal surgery under general anaesthesia. We can also provide data for infants being operated for a large ductus arteriosus.

IV.5.1.Abdominal surgery in completely stable infants

- **patients and methods.**

Twenty infants born at 35+-4.5 weeks with a birthweight of 2475 +-790 g were studied during operation under general anaesthesia at median age of 4 weeks with a body weight of 3820 +- 420g. The indication of surgery was either an inguinal hernia or a pyloris stenosis. They had stable clinical and paraclinical parameters. The general anaesthesia comprised the following drugs: atropine, fentanyl, pentothal, succinylcholine, isoflurane, atracrium, nitrous oxide, oxygen, a solution of glucose and electrolytes perfused at 4-5 ml/kg/hr. Heart rate, end-tidal CO_2, pulse oxymetry, cerebral blood flow velocities on ACA, systolic, diastolic and mean blood pressure were recorded during the perioperative time (45 +- 5 minutes). Each infant was analised during 180 cycles.

- **observations.**

The three components of blood pressure had changes similar to those observed in the CBFV and AUC. There was an increase during anaesthesia of: Sy BP= + 14%; MBP= + 20 %; DBP= + 29 %; $EtCO_2$= + 14%; Sy CBV= + 20%; DCBFV= + 100%; M CBFV= + 50%; AUC= + 50 %. During anaesthesia, the RI decrease: - 26 %. These values returned to baseline values. Heart rate increased during anaesthesia (+ 17 %) and remained significantly higher than before anaesthesia (+ 11 %). Saturation showed no longitudinal changes during the three considered periods. The observed increase of cerebral perfusion during anaesthesia evanished at the end of this. The Doppler technique, beside the other classical surveillance during anaesthesia, seems a suitable method to monitor some aspects of the cerebral circulation during surgery.

IV.5.Thoracic surgery for patent ductus arteriosus ligation in premature infants.

- **patients and methods.**

This study comprised 14 neonates born at 28.8 +- 2.5 weeks, with a birthweight of 1120 +- 320 g. They underwent thoracic surgery to ligate an important patent ductus arteriosus at 10.5 +- 3 days of age. They were, as much as possible, kept in stable clinical and paraclinical conditions. The general anaesthesia was conducted as explained before. There were three differences: i. blood pressure was monitored invasively (in minor surgery, it was by Dinamap); ii. both ACA and left middle cerebral artery were monitored by the Doppler method; iii. Just before ligating the ductus arteriosus, the infants received a bolus of fentanyl (10 microg/kg).

- **observations.**

The ligation of the ductus arteriosus induced significant and prolonged (> 12 hrs) changes in blood pressure : Sy BP= + 24% +- 23; D BP= + 36 % +- 36; M BP= + 28 % +- 26. They were also changes in CBV and RI: i. In ACA, M CBFV increased of 38 % +- 29, and the RI decreased of - 18 % +- 13.5; ii. In left MCA, MCBV increased of + 63 % +- 53, and the RI decreased of - 24 % +- 31. When comparing these 2 vessels, the left MCA evidenced more marked modifications in mean CBF and in RI of about 65 % +- 15. Hence, the surgical closure of PDA improved the cerebral perfusion, and this was more pronounced in the area perfused by the left MCA.

IV.5. Discussion

Beside the classification of drugs according to their effect on the resistance of vessels, we should add several procedures such as mechanical ventilation, chest physiotherapy, suction, general anaesthesia and surgery in these sicke babies.

In the next table, we summarize several items (states, drugs or maneuvres) and the observed circulatory effects in the babies. Although these items are given following protocols, we can observe clear effects on the circulatory parameters, either intracerebral either extracerebral. When do the story begin ? Is it the pain, is it the hypoxia, is it the failure of the cardiac pump or the lungs, up to where have the reserve mechanims been used ?

For examples:

- During general anaesthesia in completely stable infants, clear modifications of parameters of intracerebral and extracerebral circulations can be demonstrated.
- That was also the case in the situations of infants treated for hypotension, for respiratory distress with surfactant, for PDA with surgical ligation.

This underlines the feasibility and the interest of using the Doppler technique when whishing to have a look on cerebral circulation .

Items	Observed circulatory significant changes in babies
Oxygen (with controlled delivery be SaO2 abd pO2)	None
Dexamethasone	Increase in blood pressure and in CBFV
Dopamine, dobutamine	Increase in cardiac output and CBFV
Phenobarbitone (slow infusion)	None
Midazolam	Decrease in blood pressure and CBFV
Lorazepam	None
Diazepam	None
Theophylline	None
Indomethacin	+++ See text
Fentanyl (in presence of a correct blood pressure)	None (yes if blood pressure borderline or insufficient)
Nifedipine, nimodipine	Increase in CBFV
High frequency oscillatory ventilation	None (if there is a strict follow of blood gases, lungs volumes and BP)
Surgery	+++ see text
General anaesthesia	+++ see text
Cerebral edema	+++ see text
Ventricular dilatation	+++ see text
Albumin infusion	+++ see text
Intrauterine growth retardation	+++ see text
Acute respiratory distress syndrome	+++ see text
Persistance of ductus arteriosus	+++ see text
Surfactant administration	+++ see text
Prolonged oxygen dependency	+++ see text

On the other hand, *when looking at the effects of drugs on the cerebral circulation,concerning some treatments being used in unstable infants for different reasons, we can make the following points:*

1. In unstable neonates having to be sedated, midazolam should be avoided, due to its effects on CPP which is already in the low ranges in sick neonates . Diazepam or lorazepam should be used instead .

2. Before using drugs potentially modifying the cerebral and extracerebral haemodynamics, treat first the hypotension by colloïds (much efficient) or inotropic agents before using drugs such as surfactant or fentanyl;

3. and also give slow (in 30 to 60 min or even longer) infusions of phenobarbitone, morphine, magnesium sulfate, nifedipine, indomethacine or ibuprofene, theophylline or cafeine .

Gathered numbers for the references (see details at the end of the book) for chapter IV: The effects of drugs:

2,4,10,28,32,33,38,39,4051,57,59,60,62,69,72,77,78,83,91,92,98,99,101,102,105,112,118, 122,123,124,125,126,132,140,143,145,147,152,158,164,167,170,174,179,180,182,183,185 ,188,192,193,198,204,209,210,211,214,217,220,222,230,231,232,236,239,241,242,244,25 4,257,258,263,270,274,275,276,278,279,282,288,292,293,295,296,297,298,301,307,308,3 09,315,318,323,326,327,329,332,341,348,351,353,354,361,362,369,370,384, 385,399,407 .

CHAPTER V. The patency of the ductus arteriosus.

1. Assessment by Ultrasounds.

2. The medical treatment.

3. Discussion

V.1.The assessment of the patent ductus arteriosus by ultrasounds and by the Doppler method.

The patency of the ductus arteriosus (PDA) is a frequent disturbing situation in the sick preterm infants. In the tiny babies, the significant PDA (where a treatment has to be done: fluid restriction, indomethacin, ibuprofene, surgical ligation) has an incidence of around 50 %. This left-to-right shunt has important effects on cardiac and pulmonary functions, and also on the perfusion of, among other tissues such as the brain, the kidney and the digestive tract. The ill preterm infants, with their cardiovascular instability, are less able to maintain a good systemic blood pressure and cerebral perfusion, and this is more pronounced when a large PDA develops and adds an increase of the left ventricular output. Indeed, Qd have been reported to be as high as 70 ml/kg/min (going up to 100) in the presence of a significant PDA. Its stealing effect has important consequences on these organs. Abnormal cerebral blood flow patterns due to the PDA are well documented in the literature, as are their influenceon haemorrhagic and ischaemic lesions.

The persistence of the ductus arteriosus (PDA) can be followed by several parameters recorded by ultrasounds and the Doppler analysis: i.the systemic (Qs) , pulmonary (Qp) and the ductus blood flow (Qd) ; ii. the diameters of aorta, left ventricle, left atrium, pulmonary artery and ductus arteriosus; iii. the left ventricle ejection times; iv. the anteverse and reverse area under the curve on the left carotid or R/A Lct.

Table V.1. Criteria of a significant patent ductus arteriosus.

Ratios	values for a significant PDA
[systemic / ductus] blood flow	< 3.5
[Lventr / Aorta] diameter	> 2.1
[L Atr / Ao] diameter	> 1.4
[Rev / anter] AUC left carotid	> 0.14

(systemic blood flow ml/kg/min = 277 - 10.4 weight kg or = 70.3 + 217 weight kg).

We conducted a prospective study on 55 patients having, at birth, a gestational age of 33 weeks (SD = 3.9), a body weight of 1902 g (SD = 795), a body length of 43.5 cm (SD = 5.2) and a head circumference of 30.1 (SD = 3.2). We made a longitudinal analysis of their PDA by the above mentioned parameters, and also of their blood pressure and of their blood velocities on the anterior and the middle cerebral arteries.

A total of 205 measures were done between 2 and 10 days of age (median age: 5.8 days). Overall, 50.2 % had a significant PDA. In babies not having a PDA, the Qp/Qs = 1.17, and the 95 % IC = 1.01-1.33.These babies had a ratio R/A LCt = 0.063, and the 95 % IC = 0 - 0.25.

In those babies having a significant PDA, beside the other above mentioned parameters who were positive, we found an ***interesting correlation between the Qp/QS and ductal flow (DF ml/kg/ min with the Reverse/Anteverse ratio in Left carotid*** :

$$Qp/Qs = 0.869 + 4.614 \; R/A \; Lct \; (\; r = 0.988, \; p = 0.0002 \;)$$

$$DF \; ml/kg/min = 32.3 + 553.7 \; R/A \; Lct$$

With a considered abnormal Qp/QS ratio if > 1.4, the cutoff point for R/A is 0.14. In other words, the Doppler analysis of blood flow velocities on the either common or internal left carotid artery can help the clinician to quantify the left-to-right shunt due to a PDA. The stealing effect of the PDA on the CBFV is proportional to Qp/Qs and to R/A Lct ratios. The Doppler stethoscope finds another interesting clinical place .

V.2. The medical treatment of the PDA.

In those infants with a significant PDA, the medical treatment with indomethacin, when fluids restrictions is not sufficient, is largely used. This drug can reduce the cerebral blood flow and the cerebral blood flow variabilities due to systemic haemodynamic changes. In our population of preterm infants having to be treated by indomethacin because of a significant PDA, we followed the effects of that drug on both brain and systemic haemodynamics. The duration of analysis was 5 hrs (ranges: 1.4 - 8.6 hrs). The values of CBFV concerned the left MCA.

Table V.2.The observed changes in haemodynamic changes in babies treated by indomethacine for a significant patent ductus arteriosus.

	averaged baseline values (n = 37)	Averaged changes observed expressed in % of baseline values (mean +- SD)
SBP torr	45+- 10	2 +-13
DBP torr	24+- 3	17 +- 15 (p < 0.01)
MBP torr	34 +- 9	5 +- 7
Mean CBFV cm/sec	6.5+-3.4	62 +- 41 (p < 0.01)
	0.93+-0.08	-14 +- 1.4 (p < 0.01)
Act msec	69+-19	37 +- 6 (p < 0.01)
DcT msec	145+-53	14 +- 9

The significant modifications observed were an increase of the diastolic blood pressure, an increase of the mean mean blood flow velocity, a decrease of the resistance index together with a increase of the acceleration time. These data can be explained by the observed decrease of the ductal flow, a more efficient systemic blood volume and a better possibility for the left heart ventricle to eject a certain blood volume to the brain.

V.3 Further reflexions on the relationships between the systemic and the brain haemodynamics.

The relations between the systemic and the cerebral haemodynamics is a fascinating problem in intensive care medicine. In the neonatal period, owing to the incidence of respiratory difficulties and the presence of the ductus arteriosus, this pathophysiology becomes very particular.

If we consider the different curves of blood pressure in the literature, it is possible to extract from them the following points:

➔ in the curves correlating the blood pressure to body weight: whatever the way to express the values (centiles, mean and SD, etc...), the [middle/lowest or highest/middle values at birth] ratios are about 1.4 +- 0.06 and remain constant.

➔ there are normal fluctuations over time (minutes or hours) of the blood pressure and these remain < 0.5 % of baseline values. Interestingly, it decreases as the body weight increases (for instance, at 500 g it is comprised between 0.3 - 0.4 % from baseline; at 1500 g, these are between 0.23 0.33 % from baseline. That is probably reflecting the maturation of control by the autonomous nervous sytem.

➔ in the curves correlating the blood pressure to gestational age, there are differences between the values reported in utero and postconceptionally ages. The in utero values are roughly proportional to solely the gestational age (SD = 1.1), and the postconceptional values are proportional to GA + 16 (SD= 1.2). The extrauterine life fingerprints the systemic circulation.

> **Hence, for these reasons, it is very important to be clear about the choosen referential curves.**

➔ beside the importance of the quantitative values of the three parameters of blood pressure (systolic, diastolic and mean values), the quantitative fluctuations (minute per minute) of these parameters should be displayed in their trends by the monitors, and the alarms settings should concern also these parameters. That surveillance seems interesting in the approach of the pathophysiology of the most important acquired brain injuries in newborn infants.

<u>Gathered numbers for the references (see details at the end of the book) for chapter V:</u>
<u>the patency of ductus arteriosus</u>:

8,28,34,39,40,72,90,91,98,105,119,132,144,147,168,188,191,192,211,213,216,226,228,230,2
39,249,251,253,257,271,272,279,282,293,296,317,318,328,330,335,342,344,346,356,357,35
8,369,375,387,389,398,403,

VI. Clinical conditions possibly influencing the intracranial pressure

1. The intracranial pressure

2. The cerebral edema.

3. The post-haemorrhagic ventricular dilation

4. Discussion.

V.1. The intracranial pressure (ICP).

The intracranial **volumes** are represented by the cerebral mass (70 %), the blood mass (10 %), the cerebrospinal fluid or CSF mass (10 %), and the combined or separated possible variations of these these parameters for functional reasons during time (10 %). The cerebral mass , in normal condition of growth in a given fetus or newborn, is representing about 14-16 % of body weigth (and even more in cases of growth retardatio). As far as the possible variations of blood mass and CSF during time are concerned, the meticulous observations of the **intracranial pressure** curve show a quite stable line with fairly small ondulations around the baseline, and beside these, more obvious variations due to modifications of blood pressure (called A or large waves) or of pCO2 (called B or small waves).

The **cranial compliance** relationship (dV/dP) is < 1 cm3/ 3 mmHg.

The CSF production is estimated at 0.42-0.56 L/day/1.73 m2 or 6 - 8 ml/kg/day, and that volume is coming for 60 % from choroid plexuses secretions, and for 40 % from extracellular produced fluid.

> The ICP = Mean Arterial Pressure - Cerebral Perfusion Pressure
>
> or
>
> cerebral perfusion pressure = mean arterial pressure - ICP

The invasive measurements of ICP, MBP and CPP show a close correlation with the gestational age:

< Invasive ICP mmHg = 0.07 GA weeks - 1.7 (SD=10 %; r2 = 0.82).

Usually, the ICP is considered to be normal if it is below 6 mmHg, and a value above 12 mmHg is requiring a treatment. The ICP evaluations, either by (lumbar, subarchnoid or ventricular) punctures or by (from fontanometry or Doppler) estimations are hence an important aspect during the circumstances of birth asphyxia, cerebral edema, intraventricular haemorrhage, ventricular dilatation or hydrocephalus.

< invasive MBP = 0.78 GA + 9 (SD=2.13).

< invasive CPP = 1.14 GA - 2 (SD=15%; r2=0.95).
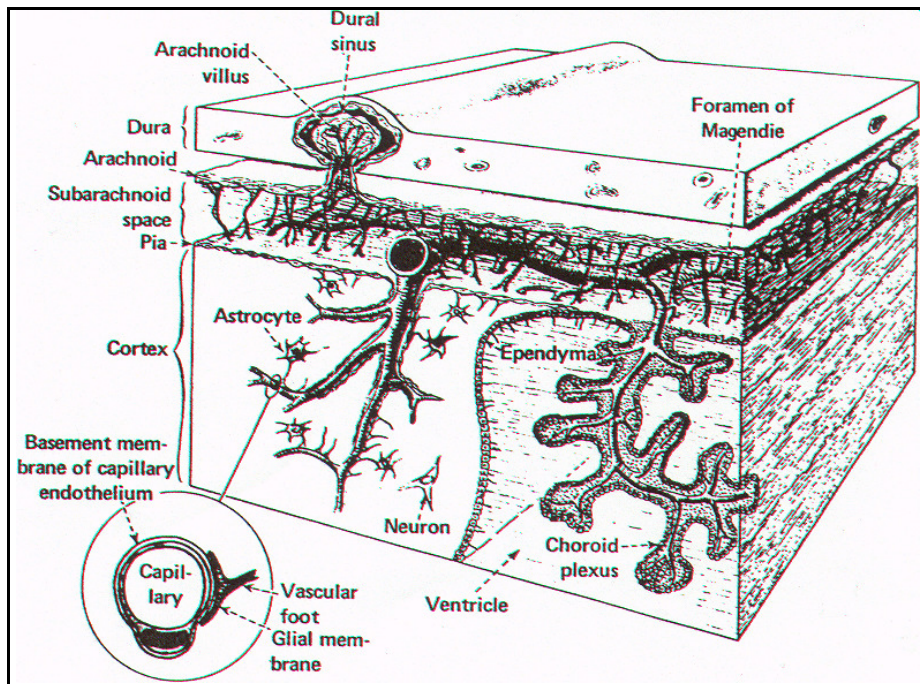
(modified after Chusid).

Indicative values in normal conditions for intracranial pressure= ICP, cerebral perfusion pressure=CPP and mean arterial blood pressure = MBP (see before for normal variations of MBP):

GA weeks	ICP torr	CPP torr	MBP torr
26	< 2	> 20	> 23
29	< 2.4	> 26	> 29
32	< 2.8	> 30	> 33
35	< 3.4	> 34	> 38
38	< 3.8	> 38	> 42

The resistance to cerebral blood flow is the result of different parameters, mainly the viscosity of blood (with an haemoglobin level higher than 23 g / dL) and the vasomotor tone. This latter is major in practice, and it is varying mostly in the vascular tree located after the circle of Willis.

Our studies looking at the correlations between cerebral blood flow velocities, cerebral perfusion pressure and intracranial pressure did concern two series of babies. Direct measurements of ICP from the subarachnoid space were correlated to CBFV in ACA, left and right MCA; systolic, diastolic and mean blood pressures; and also to the derivated indices of perfusion (AUC), of impedance to pulsatile flow (PI and RI), of perfusion homogeneity (see Chapter I)..

V.2. The cerebral edema after severe birth asphyxia

 There were ***term babies with asphyxia or acute post-hypoxic encephalopathy*** (n = 18, GA of 40 +- 1.5 weeks, 3280 +-370 g). ICP and CPP had values of 8 +- 3 and 43 +- 9 mmHg respectively..

 We found a significantly intrahemispheric loss of perfusion homogeneity at the expense of the area depending of he ACA, mainly on the left side, without any abnormality of other parameters.

In term asphyxiated neonates, we advice to calculate the ratio of AUC (ACA/LMCA) rather to limit the assessment to any resistance or impedance to pulsatile flow, as the area of perfusion depending of ACA is particularly at risk in these infants.This ratio should be comprised between 0.73 - 0.87 (95 % CI).

V.3. The post-haemorrhagic ventricular dilatation

There were ***preterm babies with post-haemorrhagic ventricular dilatation*** (n = 34, GA of 28.5 +- 2 weeks, 1100 +- 420 g). ICP and CPP had values of 8.7 +- 5 and 40 +- 11 mmHg respectively. Here, we found a slight increase of ICP, and none significantly changes of the different other measured or calculated parameters. There was a marked trend however of a decrease of the intrahemispheric and interhemispheric ratios: the area of perfusion of ACA and of left MCA tended to be lower.

Global view of major arteries in brain (modified after Netter)
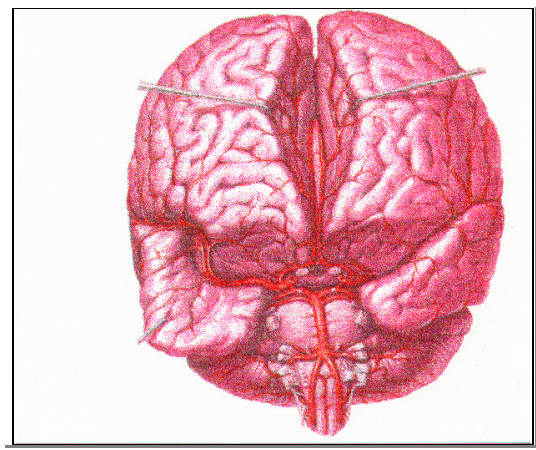
In preterm infants having a post-haemorrhagic ventricular dilatation (according to Levene's ventricular index), we advice to monitor the indices of intra- and inter-hemispheric perfusion homogeneity: these should be comprised between 0.73 - 0.87 and 0.7 - 1.3 respectively (95 % CI).

In both groups, there were highly significant correlations between in vivo direct measurements of CPP and ICP, and the calculated values of these parameters.

One has to use either RI or PI AND the AUC of three vessels (ACA, left MCA and right MCA) together with arterial mean blood pressure.

-> the best correlation is :

CPP mmHg = -2.33 + 4.93 RI ACA - 1.27 RI RMCA - 1.12 RI LMCA - 0.0034 AUC ACA - 0.00075 AUC RMCA + 0.0015 AUC LMCA + 0.88 MABP (r = 0.927).

-> an acceptable correlation is:

ICP mmHg = - 0.704 + 0.0045 AUC ACA + 0.00065 AUC RMCA - 0.00162 AUC LMCA + 0.133 MABP (r = 0.585).

Gathered numbers for the references (see the details at the end of the book) for chapter VI:The intracranial pressure: 1,15,37, 151c, 152,159b,196,197,198,209,236,237,250,269,290,303,311,354,358,361,380,382,384,392,396, 397.

Chapter VII. The fetal brain

1. In conditions with normal fetal growth

2. In conditions with retarded fetal growth

VII.1.The fetal brain in conditions with normal fetal growth

It is evident that many conclusions reported here are coming from studies in physiology and described in excellent textbooks or related articles concerning the fetal life and physiology. During fetal life, the studies have shown the relationships between the ability of the placenta to provide oxygen and nutrients to the fetus (and these are correlated to the hemodynamic capacities of the placenta) and the fetal growth in its several aspects: increase in body weight, in body length, in head circumference, and in other tissues (muscles, lungs, bones, etc ...). The different vessels investigated by the obstetrician are the placental vessels, the umbilical vessels, the aorta, the renal artery, the common and internal carotid artery, the coronary and the (anterior and middle) cerebral arteries. The used indices are those described in the chapter concerning the technique: the Systolic/Diastolic ratio or S/D, the Resistance index (RI or Pourcelot index = S-D/S), the pulsatility index (PI or Gossling index = S-D/M). The area under the curve is not being used in this area. However, the flow is being calculated, mainly in the umbilical vessels.

The main interesting conditions are:

- The follow-up of the fetal growth in normal conditions;
- The follow-up of the fetus having an abnormal (restriction or too important) growth;
- The follow-up of the fetal growth in a mother having an hypertension;
- The follow-up of the fetus at risk of having any abnormalities (defect in anatomy, in metabolism);
- The follow-up of the fetus at risk of having a blood viscosity (twin-to-twin transfusion);
- The follow-up of the fetus in any mother at risk of giving birth prematurely;

The gradual decrease of placental vascular resistance (from 28 to 40 weeks) is correlated to the gradual decrease in S/D ratio. On the other hand, the umbilical flow is increasing from 26 to around 37 weeks, and then decrease from around 37 weeks to term. When reported to body weight, the umbilical blood flow (UBF in ml/kg/min) is relatively constant from 26 to around 35 weeks (at a mean value of 120 ml/kg/min) and then decrease to 90 ml/kg/min at

40 weeks. These haemodynamic facts are probably due to the observed placental fibrosis at the end of pregnancy, a phenomenon which can be followed by ultrasounds and that might be apparent earlier in abnormal pregnancies (hypertension, tobacco, infection).

It has alos been shown that these haemodynamic parameters are in correlation with the fetal state, and that the redistribution of blood flow and volume is possible within the body, in particular to the brain.

The values of S/D ratio in fetuses:

Gestational age in weeks	S/D ratio: mean (+- SD)
26	3.3 (2.8-3.8)
28	3.1 (2.6-3.6)
32	2.7 (2.2-3.2)
36	2.4 (1.9-2.9)
40	2.2 (1.7-2.7)

The values of the umbilical blood flow in ml/min:

Gestational age in weeks	UBF ml/min : mean (+- SD)
26	100 (50-150)
28	140 (90-190)
30	180 (130-230)
32	200 (150-250)
37	310 (260-360)
40	280 (230-330)

Although one can find different absolute values of these haemodynamic parameters in the literature, the important aspects are as follows:

- on one hand, the placental vascular resistance is decreasing during pregnancy, together with an evolution to fibrosis in some areas of placenta;
- the umbilical flow, on the other hand, and hence the deliveries of substrates coming from the mother to the fetus is decreasing after around 36 weeks of gestation,

explaining the decrease in velocity of gains in anthropometry of fetus at that period;

- the earlier finding of a decrease in progress of fetal anthropometry is the consequence of the abnormal placental haemodynamics. Then, the usual haemodynamic indices become abnormal. When the deliveries of mainly aminoacids, oxygen and glucose to the fetus are nearly insufficient (for approaching the needs to maintain the integrity of cells), then redistribution of blood flow within body (trying to preserve the blood flow to the brain, the heart and the adrenal glands, hence reducing the blood flow to tissues like skeletal muscles, adipose tissue, kidney and abdominal viscera) is possible to some extent by decreasing the vascular resistance in vessels like aorta, coronary and brain arteries, but also by increasing the vascular resistance in other vessels going in the so deprivated of blood flow organs.

- Before the haemodynamic parameters show values leading to a diagnosis of vasoconstriction or vasodilation, the head circumference will maintain an acceptable progress, but the gain in body weight (calculated from measurements of body parts including tissues slowly deprived in flow and deliveries of substrates) will decrease.

- This fetal adaptation and faculty of autonomy is possible if the autonomous part of the nervous system is able to increase its metabolic work (controlling the blood flows and deliveries of metabolites). The normal variability of work (traduced by rythmicity in states of alertness or calibers of arteries, changes in frequencies of heart beats or respiration, global movements, bladder emptying) is gradually replaced by a loss of variability (and hence more monotony). At nearly the end of reserve of the haemodynamic response (vasodilation in the preserved organs), the global body of the fetus is in danger of asphyxia and death.

For all these reasons, the haemodynamic surveillance of the fetus by the Doppler method has, since many years, a tremendous importance during the entire pregnancy, and that includes the umbilical vessels and the placenta.

VII.2.In conditions with retarded fetal growth

When the growth has been compromised because of chronic insufficient deliveries of oxygen and glucose during fetal life, it is obvious that an added reduction of these deliveries of substrates in a difficult birth induces a "birth asphyxia". These high risk pregnancies of fetal death or birth asphyxia and its developmental consequences are since many years being carefully monitored in perinatal centers in order to avoid their dramatic complications. It must be noticed that retarded growth is observed in about 30% of babies born with a birth weight below 1000g, and that babies born very prematurely will experience a restriction of their growth in also about 30 % of cases. Hence, restriction or retardation of growth is concerning fetal and postnatal growth.

- **Synthesis of pathophysiology**

  The global oxygen fetal consumption is around 6 ml/kg/min, and the CBF is providing the oxygen demands of the brain (around 3 ml/100g/min. See the table II.2 for more details). The chemical properties of fetal hemoglobin and the natural increase of hemoglobin level in the fetus are the conditions to insure these demands. If its integrity is in danger for whatever reason, several mechanisms are in place to continue that provision, even if we have to distinguish the acute or chronic mode of reduction in oxygen delivery. One of these is for examples the redistribution of blood flow within the body, but further vasodilation which can be observed by the Doppler method in utero. As pO2 in utero is relatively low (25-30 mm Hg) compared after birth (above 60 mm Hg), one can observe a relative normal vasoconstriction in brain during the early hours after birth for that increase in pO2. In the cases of chronic placental insufficiency (for delivering O2 and other substrates to the fetus), body growth will reduce its velocity in the fetus, and this one will also have to increase its hemoglobin level. It is not surpising to observe in that situation a relative high cerebral/body mass ratio, and a variable degree of polycythaemia, and these factors are important to keep in mind for the reasons explained in the chapter 2.

- **the Doppler examination very early after birth**

  In this type of pregnancy, the obstetrician might firstly record abnormalities of flow velocities in umbilical vessels and fetal aorta, after a vasodilatation in fetal brain. After birth, that can also observed by the pediatrician if the oxygen reduction in utero was

relatively long (more than 6 hrs). If not, that vasodilatation is replaced after birth by either the relative early vasoconstriction or by a "normal" index of impedance to flow.

- **the Doppler examination to assess the health of the autonomous nervous tissue**

The autonomous mechanisms, coming from the autonomous nervous structures and from the endocrine functions (to which we need to add the neurotransmitters in central structures) have the role of adapting the blood flow and the substrates deliveries to the different organs in conditions normally changing during the day, the position of body, the alert / sleep states. These mechanisms are to some extent present at birth provided that:

- the fetal period arrive at term;
- without any influence of certain drugs coming from mother;
- ther are none episodes of hyper- or hypo-glycaemia;
- there are none episodes of hypoxaemia;
- there isn't a general or even peridural anaesthesia in mother;
- there isn't a significant malformation;
- there isn't a birth asphyxia, nor a significant prematurity (< 35 weeks);
- there isn't an intrauterine growth reduction or retardation or excess;
- there isn't a polycythaemia.

If one of these several conditions are added to the fetal course, the adaptative ability to adjust the cardiac output, the blood pressure, the respiration, the body temperature, the blood glucose level, the mesenteric blood flow to respond the metabolic demands of tissues might be impaired. These aspects are the reflection of the observed instability of the haemodynamic parameters in our population (see chapter 3).

In practice, on should remind that in cases of
- intrauterine growth reduction or retardation,
- prematurity
- diabetic pregnancy,

the instability of these parameters concerning the circulation can be monitored by the Doppler method concerning the circulation.

- **the Doppler method to assess the auto-regulation of the mesenteric blood flow**

We and other authors described a method to assess the mesenteric blood flow velocities who are correlated to mesenteric blood flow. Even if this is obviously not concerning the brain, we summarize here the important points concerning the mesenteric blood flow, because the sick neonate has frequently to be assessed in its digestive function.

- The mesenteric blood flow auto-regulation is depending on the effects of several hormones secreted by the digestive tract, and can be observed in normal conditions after 4 days of extra-uterine life (probably because of combined effects coming from the catecholamines surge and the ductal shunt).

- That adaptation is delayed in several conditions such as: a mother treated by beta-blockers, a mother taking illicit drugs, a reduction of fetal growth, a prematurity, a birth asphyxia, an hemoglobin level higher than 22 or lower than 6 g/100 ml, the presence of an arterial umbilical catheter, repetitive episodes of hypoxia, a circulatory failure, a blood osmolality higher than 350 mOsm/L.

- When the clinician has to feed a baby in those conditions, it is not always easy from the clinical examination to know if the digestive tract is ready to be fed or, more precisely if its blood flow auto-regulation (reflecting the presence of adapting mechanisms) is present . In that case, the analysis of blood flow velocities in the superior mesenteric artery can help the clinician.

- One can measure the mean velocity in baseline conditions. Then 0.5-1 ml of milk is given (orally or by gastric tube). After an episode of 15 minutes following this stimulus, we repeat that measure. If we observe an increment of 28 % or more in mean velocity, the mesenteric blood flow auto-regulation is present with an high probability. On the other hand, if we observe a decrease of more than 30 %, the mesenteric blood flow is in precarious state and the probability of an injury of the digestive tract epithelium is high. This method, described by Fang and coll. has our preference.

- One can also measure the mean velocity or the resistance index:

- V mean cm/s = 0.53 days + 13 (sd: 2.3) or V mean cm/s = 10 body weight in kg + 38 (sd: 13);

- RI = 0.6 – 0.9.

Gathered numbers for the references (see details at the end of the book) for chapter VII: The intrauterine growth retardation, fetal and neonatal aspects:
11,12,14,18,19,37,73,80,81,84,85,93,110,159b,161,181,189,196,203,212,213,224,240,287,300,338,339,358,376,377,378,379,384,386,391,400,401,402.

Appendix 1: The studied population:

the total number of patients is 514.

- Controls   = 318
- Respiratory distress syndrome   = 49
- Prolonged oxygen dependency   = 8
- Intrauterine growth retardation   = 21
- Intra- and peri- operative periods   = 34
- Asphyxia or posthypoxic encephalopathy   = 23
- Surfactant administration   = 12
- Cerebral ventricular dilatation   = 14
- Drugs for PDA, inotropics   = 35

Appendix 2. Relevant indexed words.

Relevant words are given by alphabetical order and the number in parentheses refer to the corresponding pages.

- Acceleration time (13,21)
- Area under the curve (13,21)
- Attenuation (11)
- Blood-brain-barrier (34,68)
- Blood pressure (52)
- Brain arteries (17,25,68)
- Cascades (35)
- Cerebral blood flow autoregulation (22,29,30,31)
- Cerebral blood flow (31)
- Cerebral blood volume (31)
- Cerebral de livery of a susbstrate (28)
- Cerebral mass (27,46)
- Cerebral metabolic rate (28)
- Cerebral perfusion pressure (65)
- Continuous wave (18)
- Curie principle (10)
- Deceleration time (13,21)
- Doppler principle (10)
- Ductus arteriosus (60 and ctd)
- Extraction rate (28)
- Fetal Doppler (71 and ctd)
- Fetal growth (74)
- Grey matter (28)
- Integrity of cells (32)
- Intracranial pressure (65)
- Maximum frequency envelope (12)
- Mesenteric flow (76)
- Perfusion homogeneity (14,15)

- Perfusion pressure (14,15)
- Pulsed wave (18)
- Qp / Qs ratio (60)
- Pahtways (43,44,45)
- Refraction (11)
- Resistance to flow indices (13,19,22,26)
- Sample volume (18)
- Transducer (10,12)
- White matter (28)
- Windows (16)

Appendix 3. The equipments, techniques and and the quick index for the used formulas.

- <u>The types of equipment</u>
1. Continuous Device: here, the 2 transducers (one for emission and one for reception) are located side by side. They continuously record the signals coming from all moving red cells from all layers in the considered vessel. The probes are flat and pencil-like
2. Pulsed device: here, the same transducer is on one moment emitter and in an other moment receiver from sampled and selected depths gated moving red cells in a selected distance from the transducer (that is called the sample volume).
3. These devices give different absolute values of blood velocities, the difference is about 20% greater values for the pulsed probe, as here it is the more rapid central layers who are considered , where all layers are considered with the continuous probe.
4. In the cardiologic and obstetrical types of instruments, both anatomical and Doppler aspects are considered ("combined Doppler and ultrasounds"), and the probes are the pulsed type. The sample volume is particularly precise, for the anatomy is diplayed.
- <u>The practical aspects of the technique</u>
1. The appropriate probe (type and frequency): one should use the lowest frequency for Doppler examination, and either the flat or pencil-like probe according the anatomical region and the need or not to observe for a prolonged time the blood velocities (see text for our recommendations).
2. One should pay attention to record the different parameters necessary to make the calculations, on one or multiple arteries.
3. One should also pay attention to record the different extracerebral parameters to allow a global interpretation of the situation.
4. The recording might be difficult because of the movements, the crying or air present in the lungs and in the bowel.
- <u>The formulas (and the corresponding pages for description):</u>
1. Christian Doppler formula (p 10);
2. Blood flow calculation (p 11);

3. Poiseuille formula (p 13);

4. Resistance indices (p 13);

5. Resistance transmission indices (p 14);

6. Intrahemispheric and interhemispheric indices (p 14);

7. Normal values equations (p 19-23);

8. Cerebral mass (p 27);

9. Cerebral blood flow autoregulation and independency (p 22 , p31, p 40);

10. Cardiac output calculation (p 40 ,41, 48);

11. Cerebral blood flow calculation (p 40, 48);

12. Mean blood pressure and gestational age (p 53);

13. criteria for a significant patent ductus arteriosus (p 60);

14. Calculation of pulmonary over systemic blood flow or Qp/Qs (p 61);

15. Calculation of intracranial pressure (p 66 , 70);

16. Calculation of cerebral perfusion pressure (p 70);

17. Mesenteric blood flow and mesenteric blood flow indepedency (p 77);

__Appendix 4. The records' scheet advices__

1. The formulas given in this manuscript give the possibility to build graphs (mean and intervals for a given parameter according to body weight, gestational age or postnatal age);

2. The normal values should be reported beside the column of results.

3. The record should include the name of the vessels, the measured and calculated

intracerebral and extracerebral parameters, and the clinical condition of the patient: the gestational age, the postnatal age, the precise epochs of examination, the respiratory and circulatory status, the blood pressure, the blood gases, eventually the glycemia and the hematocrit, the drugs (including the oxygen) given, the state of alertness or sleep ;

4. The interpretation of results should concern the impedance to flux, the indices of perfusion. From the description of results and from the integration of these to the present pathophysiology, the technique should help the clinician in his/her decision.

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Appendix 6. Practice illustrated
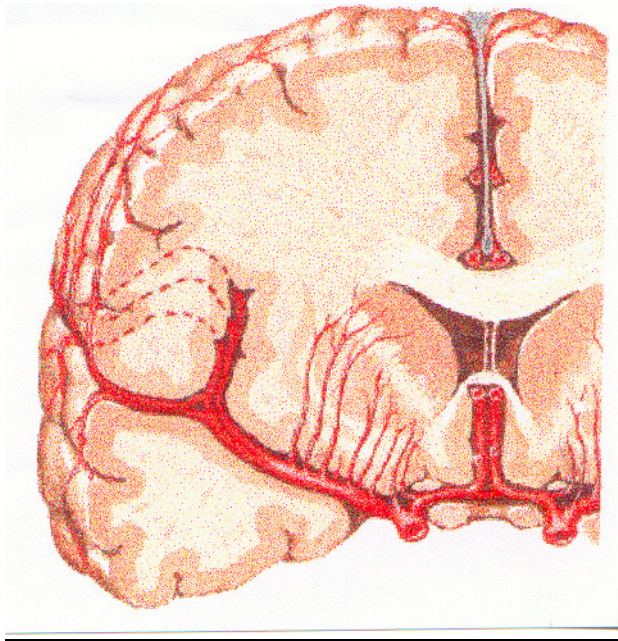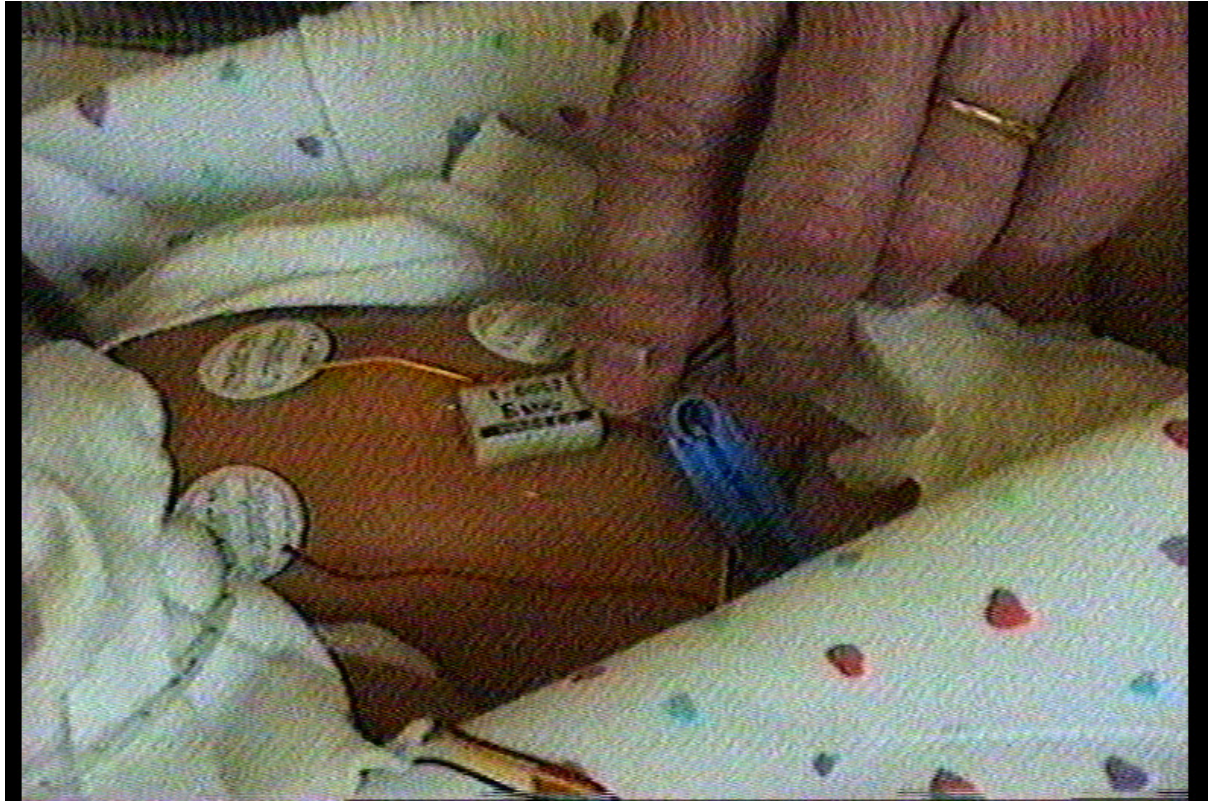
- Anterior cerebral artery approach
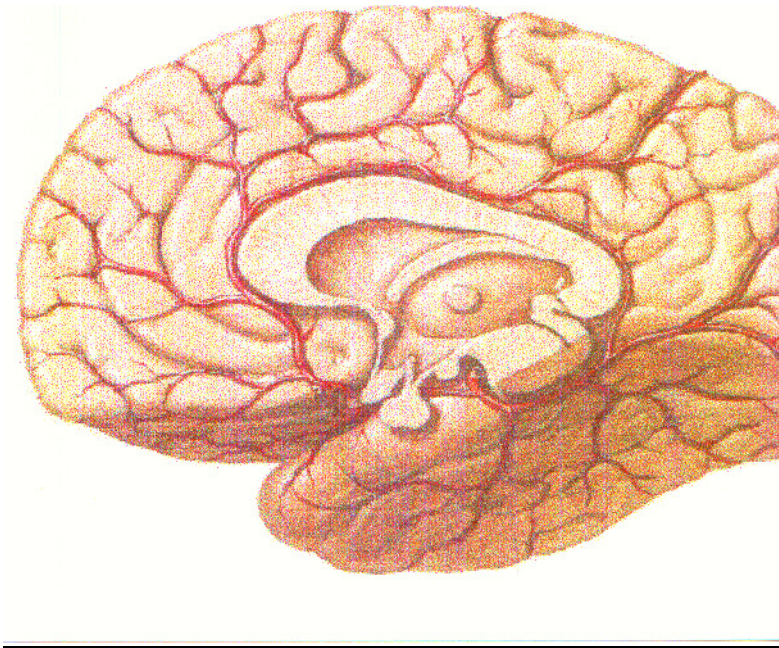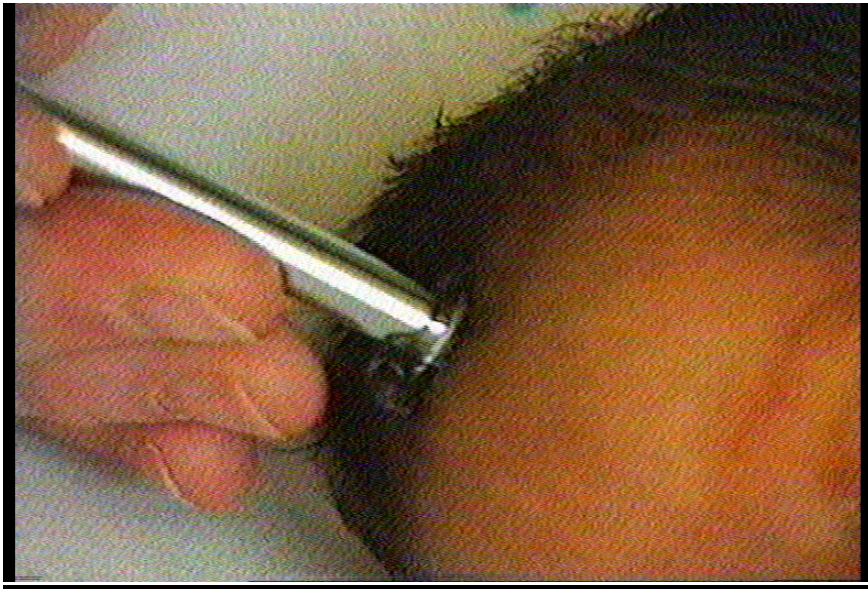
- middle cerebral artery approach

- left carotid approach

- superior mesenteric artery approach

References

1-AASLID R. Transcranial Doppler sonography. Springer-Verlag, 1986, 177 p.

2-ABDEL-RAHMAN AM, ROSENBERG AA. Prevention of intraventricular hemorrhage in the

premature infant.   Clinics Perinatol 1994, 21:505-519.

3-ADINOLFI M. Infections diseases in pregnancy, cytokines and neurological impairment : an hypothesis. Develop   Med Child Neurol 1993, 35, 549-553.

4-ALLAN WC, RIVIELLO JJ. Perinatal cerebrovascular disease in the neonate.
Pediatr Clin North America 1992, 39, 621-650.

5-ALMSTROM H, AXELSSON O, CNATTINGUS S, EKMAN G, MAESEL A, ULMSTEN U, ARSTRO M K,   MARSAL K. Comparison of umbilical-artery velocimetry and cardiotocographic for surveillance of small-for-gestational-age fetuses. The Lancet 1992, 340, 936-940.

6-ALTMAN DI, POWERS WJ, PERLMAN JM, HERSCOVITCH P, VOLPE SL, VOLPE JJ. Cerebral blood flow   requirement for brain viability in newborn infants is lower than in adults. Ann Neurol 1988, 24, 218-226.

7-ALTMAN DI. Cerebral blood flow in premature infants: regulation, measurement and pathophysiology of   intraventricular hemorrhage. In: Polin RA, Fox WW (editors): Fetal and neonatal physiology Vol2, WB Saunders   Company, 1992, pp 1587-1597.

8-ALVERSON DC, ELDRIDGE MW, JOHNSON JD, BURSTEIN R, PAPILE LA, DILLON T, YABECK S,   BERMAN W. Effect of patent ductus arteriosus on left ventricular output in premature infants. J Pediatr 1983, 102, 754-757.

9-AMIEL-TISON C, STEWART A (editors). The newborn infant one brain for life. Les Editions INSERM, 1994, 307 p.

10-ANDERSEN K, JENSEN KA, EBBESEN F. The effect of phenobarbital on cerebral blood flow in newborn infants with foetal distress. Eur J Pediatr 1994, 153:584-587.

11-ARABIN B. Doppler blood flow measurement in uteroplacental and fetal versus. Springer Verlag, 1990, 148 p.

12-ARABIN B, MOHNHAUPT A, BECKER R, WEITZEL HK. Comparison of the prognostic value of pulsed Doppler blood flow parameters to predict SGA and fetal distress. Ultrasound Obstet Gynecol 1992, 2, 272-278.

13-ARANDA JV, MONIN P, BEHARRY K, BAIRAM A, VERT P. The effect of endothelin-1 on the cerebrovascular response to hypoxia and hypercapnia in the newborn. Seminars in Perinatol 1992, 16:196-199.

14-ARBEILLE P, BODY G, SALIBA E, TRANQUART F, BERSON M, RONCIN A, POURCELOT L. Fetal cerebral circulation assessment by Doppler ultrasound in normal and pathological pregnancies. Eur J Obstet Gynecol Rep Biol 1988, 29, 261-273.

15-ARCHER LNJ, LEVENE MI, EVANS DH. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. The Lancet 1986, 2:1116-1117.

16-ARCHER LNJ, EVANS DH, PATON JY, LEVENE MI. Controlled hypercapnia and neonatal cerebral artery Doppler ultrasound waveforms. Pediatr Res 1986, 20:218-221.

17-ARCHER LNJ, EVANS DH. Doppler assessment of the neonatal cerebral circulation. In : LEVENE MI,   BENNETT MJ, PUNT J (editors): Fetal and neonatal neurology and neurosurgery Churchill

Livingstone 1988, 162- 168.

18-ARDUINI D, RIZZO G, ROMANINI C. Changes of pulsatility index from fetal vessels preceding the onset of late decelerations in growth-retarded fetuses. Obstet Gynecol 1992, 79, 605-610.

19-ARIAS F. Accuracy of the middle-cerebral-to-umbilical-artery resistance inde ratio in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications. Am J Obstet Gynecol 1994, 171, 1541-1545.

20-ARNOLD BW, MARTIN CG, ALEXANDER BJ, CHEN T, FLEMING LR. Autoregulation of brain blood flow during hypotension and hypertension in infant lambs. Pediatr Res 1991, 29, 110-115.

21-ARTRU AA, COLLEY PS. Cerebral blood flow responses to hypocapnia during hypotension. Stroke, 1984, 15,878-883.

22-AZZOPARDI D, WYATT JS, CADY EB, DELPY DT, BAUDIN J, STEWART AL, HOPE PL, HAMILTON PA, REYNOLDS EOR. Prognosis of nexborn infants with hypoxic-ischemic brain injury assessed by phosphorus magnetic resonance spectroscopy. Pediatr Res 1989, 25, 445-451.

23-AZZOPARDI D, WYATT JS, HAMILTON PA, CADY EB, DELPY DT, HOPE PL, REYNOLDS EOR.   Phosphorus metabolites and intracellular pH in the brain of normal and small for gestational age infants investigated by magnetic resonance spectroscopy. Pediatr Res 1989, 25, 440-44.

24-AZZOPARDI D, EDWARDS D. Magnetic resonance spectroscopy in neonates. Current Op Neurol 1995, 8, 145-149.

25-BADA HS, SUMMER DS. Transcutaneous doppler ultrasound : pulsatility index, mean flow velocity, and diastolic flow velocity, and cerebral blood flow. J Pediatr 1984, 104, 395-397.

26-BADA HS, KORONES SB, PERRY EH, ARHEART KL, RAY JD, POURCYROUS M,MAGILL HL,   RUNYAN W, SOMES GW, CLARK FC, TULLIS KV. Mean arterial blood pressure changes in premature   infants and those at risk for intraventricular hemorrhage.
J Pediatr 1990, 117, 607-614.

27-BAENZIGER O, JAGGI JL, MUELLER AC, MORALES CG, LIPP AE, DUC G, BUCHER HU. Regional   differences of cerebral blood flow in the preterm infant. Eur J Pediatr 1995, 154, 919-924.

28-BAERTS W, FETTER WPF, HOP WCJ, WALTENBURG HCS, SPRITZER R, SAUER PJJ. Cerebral lesions in preterm infants afetr tocolytic indomethacin. Dev Med Child Neurol 1990, 32, 910-918.

29-BAERTS W, VALENTIN RAC, SAUER PJJ. Ophtalmic and cerebral blood flow velocities in preterm infants: influence of ambient lighting conditions. J Clin Ultrasound 1992, 20, 43-48.

30-BAENZIGER O, JAGGI JL, MUELLER AC, MORALES CG, LIPP HP, LIPP AE, DUC G, BUCHER HU. Cerebral blood flow in preterm infants affected by sex, mechanical ventilation, and intrauterine growth. Pediatr Neurol 1994, 11:319-324.

31- BAENZIGER O, JAGGI JL, MUELLER AC, MORALES CG, LIPP HP, LIPP AE, DUC G, BUCHER HU. Regional differences of cerebral blood flow in the preterm infant. Eur J Pediatr 1995, 154, 919-924.

32-BAIRAM A, BLANCHARD PW, MULLAHOO K, BEHARRY K, LAUDIGNON N, ARANDA JV.

Pharmacokinetic profiles of keto-doxapram and doxapram in newborn lambs. Pediatr Res 1990, 28, 142-146.

33-BALSAN MJ, CRONIN CMG, SHAW MD, MILLEY JR. Blood flow distribution and brain metabolism during tolazoline-indiced hypotension in newborn dogs. Pediatr res 1990, 28, 111-115.

34-BANDSTRA ES, MONTALVO BM, GOLDBERG RN, PACHEBO I, FERRER PL, FLYNN J,GREGORIOS JB, BANCALARI E.Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature   infants. Pediatrics 1988, 82, 533-542.

35-BARRINGTON KJ, RYAN AC, PELIOWSKI A, MOSKOM, FINER NN.The effects of negative pressure   external high frequency oscillation on cerebral blood flow   and cardiac output of the monkey. Pediatr Res 1987,   21, 166-169.

36-BASAR E, BULLOCK TH. Brain dynamics, 1989, Springer-Verlag, 547p.

37-BATTISTI O, ADANT-FRANçOIS A, BERTRAND JM, DETRY J, LAMBERT Y, LECART C, LOUIS J, LANGHENDRIES JP. Correlations between cerebral blood flow velocities, cerebral perfusion pressure and intracranial pressure in sick neonates.Circulation et Métabolisme du cerveau 1995, 12, 139-148.

38-BATTISTI O, ARMENGOL A, WITHOFS L, CROUGHS MO, BERTRAND JM, FRANCOIS A, LANGHENDRIES JP. Cerebral and extracerebral hemodynamics in healtly and sick human neonates. Circulation et Métabolisme du cerveau 1992, 9, 95-102.

39-BATTISTI O, DE BOE X, HUBERT P, STEVENS A, LATOURT JP, PAQUOT JP, FRANçOIS A, BERNIER V, BERTRAND JM, LANGHENDRIES JP. Cerebral blood flow velocity measurements on anterior cerebral artery during general anesthesia and minor surgery in infants. Circulation et Métabolisme du cerveau 1993, 10, 73-78.

40-BATTISTI O, DETRY J, LOUIS J, FRANçOIS A, CHEDID F, BERTRAND JM, LANGHENDRIES JP. Cerebral blood flow velocities during natural bovine surfactant therapy in very preterm babies.Circulation et Métabolisme du cerveau 1994, 11, 9-14.

40 a-BATTISTI O, ADANT-FRANçOIS A, SCALAIS E, KALENGA M, WITHOFS L, PAQUAY T, LANGHENDRIES JP, REDING B, PIERART F, JORDAN I, MATON P. The acquired brain injuries in the term and preterm babies : an update on their pathophysiology. J Pédiatr Belge 2001, 3, 216-217.

40 b-BATTISTI O, WITHOFS L , ADANT-FRANçOIS A, BERTRAND JM, KALENGA M, LANGHENDRIES JP,PIERART F, REDING B. Etude longitudinale de l'hémodynamique artérielle mésentérique chez le nouveau-né prématuré stable en alimentation entérale. Louvain Med 2002, 121, 117-123.

40 c-BATTISTI O, WITHOFS L, LATOUR JP, PAQUOT JP, KHUC T, MONIOTTE S, EGEDY M, ADANT-FRANçOIS A, BERTRAND JM,JORDAN I, KALENGA M, MATON P, LANGHENDRIES JP, PIERART F. Etude longitudinale du canal artériel chez le nouveau-né instable :intérêt du Doppler de la carotide gauche dans l'évaluation du shunt gauche-droit. Louvain Med 2003, 122,

41-BATTON DG, NARDIS EE. The effect of intraventricular blood on cerebral blood flow in newborn dogs. Pediatr Res 1987, 21, 511-515.

42-BATTON DG, RIORDAN S, RIGGS T. Cerebral blood flow velocity in normal, full- term newborns is not related to ductal closure. Am J Dis Child 1992, 146, 737-740.

43-BENSON JWT, DRAYTON MR, HAYWARD C, MURPHY JF, OSBORNE JP, RENNIE JM, SCHULTE JF, SPEIDEL BD, COOKE RWI. Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. Lancet 1986, 2, 1297-1300.

43b-BEVAN RD, VIJYAKUMARAN E, GENTRY A, WELLMAN T, BEVAN JA. Intrinsic tone of cerebral artery segments of human infants between 23 of gestation and term. Pediatr Res 1998,43:20-27.

44-BIDABE AM, FLORAS P, GIN AM, CAILLE JM. Action des morphiniques et antagonistes de la morphine sur la circulation et le métabolisme du cerveau. Circulation et Métabolisme du cerveau 1986, 3:17-27.

45-BIGNALL S, BAILEY PC, RIVERS RPA, LISSAUER TJ. Quantification of cardiovascular instability in premature infants using spectral analysis of waveforms. Pediatr Res 1988, 23:398-401.

46-BODE H, WAIS U. Age dependence of flow velocities in basal cerebral arteries. Archives Dis Child 1988, 63, 606- 611.

47-BODE H. Pediatric applications of transcranial doppler sonography. Springer-Verlag (Wien) 1988, 144p.

47b-BORSCH K, GREISEN G. Blood flow distribution in the normal human pretrm brain. Pediatr Res 1998,43:28-33.

48-BORZEIX MG, ANGIGNARD J, WEBER S, CAHN R. Débit sanguin, métabolisme cérébral et déficit neurologique résultant d une ischémie cérébral transitoire chez le primate. Circulation et Métabolisme du cerveau 1988, 5:125-130.

49-BOSE CL, LAWSON EE, GREENE A, MENTZ W, FRIEDMAN M. Measurements of cardiopulmonary function in ventilated neonates with respiaratory distress syndrome using rebreathing methodology. Pediatr Res 1986, 20,316-320.

50-BOTTOMLEY PA, HART HRJr , EDELSTEIN WA, SCHENK JF, SMITH LS, LEUE WM, MUELLER OM, REDINGTON RW. Anatomy and metabolism of the normal human brain studied by magnetic resonance at 1.5 Tesla. Radiology 1984, 151:441-446.

51-BOULARD G. Anesthésiques, débit et métabolisme du cerveau: l enjeu. Circulation et Métabolisme du cerveau 1986, 3:1-3.

52-BOULU RG. Modèles d ischémie cérébrale expérimentale: critères d efficacité des médicaments. Circulation et Métabolisme du Cerveau 1987, 4: 217-229.

53-BOULU RG, LE PEILLET E, PLOTKINE M. Effects of calcium antagonists on cerebral circulation in neonatal and ischemic conditions.Circulation et Métabolisme du cerveau 1990, 7, 133-142.

54-BOZYNSKI MEA, DIPETRO MA, MEISELS SJ, PLUNKETT JW, BURPEE B, CLAFLIN CJ.Cranial sonography and neurological examinations of extremely preterm infants. Dev Med Child Neurol 1990, 32, 575-581.

55-BRALET J. Revue critique des modèles expérimentaux d ischémie cérébrale.Circulation et Métabolisme du Cerveau 1987, 4:1-13.

56-BRAYTON MR, SKIDMORE R. Vasoactivity of the major intracranial arteries in newborn infants. Arch Dis Child 1987, 62, 236-240.

57-BRUBAKK AM, BRATLID D, OH W, YAO A, STONESTREET BS. Atropine prevents increases in brain blood flow during hypertension in newborn piglets. Pediatr Res 1984, 18:1121-1126.

58-BRUN NC, GREISEN G. Cerebrovascular responses to carbon dioxide as detected by near-infrared spectrophotometry: comparison of three different measures. Pediatr Res 1994, 36, 20-24.

59-BUCHER HU, WOLF M, KEEL M, VON SIEBENTHAL K, DUC G. Effect of aminophylline on cerebral   haemydynamics and oxydative metabolism in premature infants. Eur J Pediatr 1994, 153:123-128.

60-BURTIN P, DAOUD P, JACQZ-AIGRAIN E, MUSSAT P, MORIETTE G. Hypotension with midazolam and fentanyl in the newborn. The Lancet 1991, 337:1545-1546.

61-BUSIJA BW, HEISTAD DD, MARCUL ML. Continuous measurement of cerebral blood flow in anesthetized cats and dogs. Am J Physiol 1981, 241, H : 228-234.

62-CABANAS F, PELLICER A, GARCIA-ALIX A, QUERO J. Effect of dexamethasone therapy on cerebral and ocular blood flow velocity in premature infants studied by colour Doppler flow imaging. Eur J Pediatr 1997, 156, 41-46.

63-CADY EB, DAWSON MJ, HOPE PL, TOFTS PS, COSTELLO AM de L , DELPY DT, REYNOLDS EOR, WILKIE DR. Non-invasive investigation of cerebral metabolism in newborn infants by phosphorus nuclear magnetic resonance spectroscopy. The Lancet 1983, 1:1059-1062.

64-CAHN J, LASSEN NA (editors). New brain imaging techniques in cerebrovascular diseases. John Libbey   Eurotext, 1985, 135 p.

65-CALVERT SA, OHLSSON A, HOSKING MC, ERSKINE L, FONG K, SHENNAN AT. Serial measurements of cerebral blood flow velocity in preterm infants during the first 72 hours of life. Acta   Paediatr Scand 1988, 77, 625-631.

66-CARSON SC, HERTZBERG BS, BOWIE JD, BURGER PC. Values of sonography in the diagnosis of intracranial hemorrhage and periventricular leukomalacia : a postmortem study of 35 cases.   AJNR 1990, 11, 677-683.

67-CHATOW U, DAVIDSON S, REICHMAN BL, AKESLROD S. Development and maturation of the autonomic nervous system in premature and full-term infants using spectral analysis of heart rate fluctuations. Pediatr Res 1995, 37, 294-302.

68-CHEMTOB S, BEHARRY K, REX J, VARMA DR, ARANDA JV. Changes in cerebrovascular prostaglandines and thromboxane as a function of systemic blood pressure.Circulation Research 1990, 67, 674-682.

69-CHEMTOB S, BEHARRY K, BARNA T, VARMA DR, ARANDA JV. Differences in the effects in the newborn piglet of various nonsteroidal antiinflammatory drugs on the cerebral blood flow but not on cerebralvascular prostaglandins. Pediatr Res 1991, 30:106-111.

70-CHEUNG YF, LAM PKL, YEUNG CY. Early postnatal cerebral Doppler changes in relation to birthweight. Early Human Dev 1994, 37, 57-66.

71-CHUSID JG. Correlative neuroanatomy and functional neurology (19 th edition), Lange Medical Publications, 1985, 513 p.

72-COLDITZ P, MURPHY D, ROLFE P, WILKINSON AR. Effects of infusion rate of indomethacin on cerebrovascular response in preterm neonates. Arch Dis Child 1989, 64, 8-12.

73-CONNORS G, HUNSE C, GAGNON R, RICHARDSON B, HAN V, ROSENBERG H. Perinatal assessment of cerebral flow velocity waveforms in the human fetus and neonate. Pediatr Res 1992, 31, 649-652.

74-COOKE RWI, COSTELOE K, ROLFE P, TIZARD JPM. Measurement of cerebral blood flow in the newborn. In : Stern L, Oh W, Friis-Hansen B (Editors) : Intensive care in the newborn, II. Masson Publishing USA, 1978, 127-133.

75-COUGHTREY H, RENNIE JM, EVANS DH. Postnatal evolution of slow variability in cerebral blood flow velocity. Arch Dis Childh 1992, 67, 412-415.

76-COWAN F, THORESEN M. Ultrasound study of the cranial venous system in the human new-born infant and the adult. Acta Physiol Scand 1983, 117:131-137.

77-COWAN F, THORESEN M. The effects of intermittent positive pressure ventilation on cerebral arteria and venous blood velocities in the newborn infant. Acta Paediatr Scand 1987, 76:239-247.

78-COWAN F, WHITELAW A, WERTHEIM D, SILVERMAN M. Cerebral blood flow velocity changes after rapid administration of surfactant. Arch Dis Child 1991, 66, 1105-1109.

79-COWAN F, THORESEN M. The effects of intermittent positive pressure ventilation on cerebral arterial and venous blood velocities in the newborn infant. Acta Paediatr Scand 1987, 76, 239-247.

80-DAN DEN WIJNGAARD JAGW, VAN EYCK J, NOORDAM MJ, WLADIMIROFF JW. The Doppler flow velocity waveform in the fetal internal carotid artery with respect to fetal behavioural states. Bilo Neonate 1988, 53, 274-278.

81-DAWES GS, BORRUTTO F, ZACUTTI A, ZACUTTI A Jr (editors). Fetal autonomy and adaptation. Wiley and Sons, 1990, 186 p.

82-DE VRIES LS. Neurological assessment of the preterm infant. Acta Paediatr Scand 1996, 85, 765-771.

83-DEARDEN NM. Ischaemic brain. Lancet 1985, 2, 255-259.

84-DEGANI S, LEWINSKY RM, SHAPIRO I. Doppler studies of fetal cerebral blood flow. Ultrasound Obstet Gynecol 1994, 4, 158-165.

85-DEGANI S, PALTIELI Y, GONEN R, SHARF M. Fetal internal carotid artery pulsed Doppler flow velocity waveforms and maternal plasma glucose levels. Obstet Gynecol 1991, 77, 379-381.

86-DEL TORO J, LOUIS PT, GODDARD- FINEGOLD J. Cerebrovascular regulations and neonatal brain injury. Pediatr Neurol 1991, 7, 3-12.

87-DELMAS A. Voies et centres nerveux (10th edition), Masson, 1981,283 p.

88-DOBBING J, SANDS J. Head circumference, biparietal diameter and brain growth in fetal and postnatal life. Arch Dis Child 1978, 2, 81-77.

89-DOBBING J, SANDS J. Quantitative growth and development of human brain. Arch Dis Child 1973, 48, 757-767.

90-DOOLEY KJ. Management of the premature infant with a patent ductus arteriosus. Pediatr Clin North Am 1984, 31, 1159-1174.

91-DORREPAAL CA, BENDERS MJNL, STEEDIJK P, VAN DE BOR M, BEL F. Cerebral hemodynamics and oxygenation in preterm infants afetr low- vs high- dose surfactant replacement therapy. Biol Neonate 1993, 64, 193-200.

92-D SOUZA SW, SLATER P. Excitatory amino acids in neonatal brain: contributions to pathology and therapeutic strategies. Arch Dis Child 1994, 70, F 147-150.

93-DUBIEL M, GUDMUNDSSON S, MARSAL K. Middle cerebral artery velocimetry as a predictor of hypoxemia in fetuses with increased resistance to blod flow in the umbilical artery. Early Hum Dev 1997, 47, 177-184.

94-DUCKETT S (editor). Pediatric neuropathology. William-Wilkins 1995, 954 p.

95-DRAYTON MR, SKIDMORE R. Vasoactivity of the major intracranial arteris in newborn infants. Arch Dis Childh 1987, 62, 236-240.

96-EDELSTONE DI. Fetal compensatory responses to reduced oxygen delivery. Seminars Perinatol 1984, 8, 184-191.

97-EDWARDS AD, RICHARDSON C, COPE M, WYATT JS, DELPY DT, REYNOLDS EOR. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. The Lancet 19988, 2:770-771.

98-EDWARDS AD, McCORMICK DC, ROTH CE, et al. Cerebral hemodynamics effects of treatment with modified natural surfactant investigated by near infrared spectroscopy. Pediatr Res 1992, 32, 532-536.

99-EDWARDS AD, WYATT JS, RICHARDSON C, POTTER A, COPE M, DELPY DT, REYNOLDS EOR. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet 1990, 335, 1491-1495.

100-ELLISON P, HORN J, BROWN P, DENNY J. Continuous wave ultrasound measure of neonatal cerebral blood flow. Acta Paediatr Scand 1986, 75, 905-912.

101-ERONEN M, KARI A, PESONEN E, HALLMAN M. The effect of antenatal dexamethasone administration on the fetal and neonatal ductus arteriosus. AJDC 1993, 147:187-192.

102-ESPINOZA MI, PARER JT. Mechanisms of asphyxial brain damage, and possible pharmacologic interventions, in the fetus. Am J Obstet Gynecol 1991, 164:1582-1591.

103-EVANS DH, ARCHER LNJ, LEVENE MI. The detection of abnormal neonatal cerebral brain dynamics usingprincipal component analysis of the doppler ultrasound waveform.Ultrasound in Med and Biol 1985, 11, 441-449.

104-EVANS DH. On the measurement of the mean velocity of blood flow over the cardiac cycle using doppler ultrasound. Ultrasound in Med and Biol 1985, 11, 735-741.

105-EVANS DH, LEVENE MI,ARCHER LNJ. The effects of indomethacin on cerebral blood flow velocity in premature infants. Dev Med Child Neurol 1987, 29, 776-782.

106-EVRARD P, MINKOWSKI A. Developmental neurobiology, 1989, Nestec Ltd Raven Press, 315p.

107-FARSTAD T, ODDEN JP, BRATLID D. Effect of intraventricular hemorrhage on pulmonary function in newborn piglets. Biol Neonate 1994, 66, 238-246.

108-FENTON AC, SHORTLAND DB, PAPATHOMA E, EVANS DH, LEVENE MI. Normal range for blood flow velocity in cerebral arteris of newby born term infants. Early Human Dev 1990, 22, 73-79.

109-FERRARI F, KELSALL AWR, RENNIE JM, EVANS DH. The relationship between cerebral blood flow velocity fluctuations and sleep state in normal newborns. Pediatr Res 1994, 35, 50-54.

110-FITZGERALD DE, STUART BT. Fetoplacental and uteroplacental blood flow in pregnancy. In: Hill A and Volpe JJ (editors): Fetal Neurology, Raven Press, New York, 1989, pp 121- 137.

111-FLODMARK O. Imaging of the neonatal brain..In : LEVENE MI, BENNETT MJ, PUNT J. (Editors): Fetal and neonatal neurology and neurosurgery Churchill Livingstone 1988, 105-128.

112-FORD LM. Results of N-methyl-D-aspartate antagonists in perinatal cerebral asphyxia therapy. Pediatr Neurol 1990, 6, 363-366.

113-FRACKOWIAK RS. Cerebral energy metabolism and blood flow in normal ageing: a short review. Circulation et Métabolisme du cerveau 1987, 4:87-92.

114-FREWEN TC, SUMABAT WO, DEL MAESTRO RF. Cerebral blood flow, metabolic rate, and cross-brain oxygen consumption in brain injury J Pediatr 1985, 107, 510-513.

115-FRIIS-HANSEN B. Perinatal brain injury and cerebral blood flow in newborn infants. Acta Paediatr Scand 1985,74:323-331.

116-FRIIS-HANSEN B, LOU H, LASSEN NA. Cerebral blood flow in distressed infants.In: Stern L, Oh W and Friis-Hansen B (editors): Intensive care in the newborn II. Masson Publishing, 1978, pp.119-125.

117-FUTAGI Y, OTANI K, TAGAWA T, YABUUCHI H. Internal carotid arterial blood flow velocity in infants. Pediatr Neurol 1992, 8, 200-204.

118-GHAY V, RAJU TNK, KIM SY, McCULLOCH KM. Regional cerebral blood flow velocity after aminophylline therapy in premature newborn infants. J Pediatr 1989, 114, 870-873.

119-GHOSH PK, LUBLINER J, MOGLINAR M, YAKIREVICH V, VIDNE BA. Ligation of patent ductus arteriosus in very low birth-weight premature neonates. Thorax 1985, 40, 533-537.

120-GILBERT RD, PEARCE WJ, ASHWAL S, LONGO LD. Effects of hypoxia on isolated fetal cerebral arteries.J Develop Physiol 1990, 13, 199-203.

121-GLOPERUD JM, DELIVORIA-PAPADOPOULOS M. Cerebral blood flow and metabolism during repeated asphyxias in newborn piglets: influence of theophylline. Biol Neonate 1994, 65, 220-230.

122-GODDAR-FINEGOLD J, ARMSTRONG DL. Reduction in incidence of periventricular, intraventricular hemorrhages in hypertensive newborn beagles pretreated with phenobarbital. Pediatrics 1987, 79, 901-906.

123-GODDARD-FINEGOLD J, DONLEY DK, ADHAM BI, MICHAEL LH. Phenobarbital and cerebral blood flow during hypertension in the newborn beagle. Pediatrics 1990, 86:501-508.

124-GODDARD-FINEGOLD J, MICHAEL LH. Brain vasoactive effects of phenobarbital during hypertension and hypoxia in newborn pigs. Pediatr Res 1992, 32:103-106.

125-GOLDEN J, BEJAR R, LOHRER R, MERRITT TA. Acute changes in cerebral blood flow velocities (CBFV) and intraventricular bleeds (IVH) afetr exosurf (Surf) administration. Clin Res 1992, 40, 65A.

126-GOLDSTEIN M, STONESTREET BS, BRANN BS, OH W. Cerebral cortical blood flow and oxygen metabolism in normocythemic hyperviscous newborn piglets. Pediatr Res, 1988, 24, 486-489.

127-GOPLERUD JM, DELIVORIA-PAPADOPOULOS M. Cerebral blood flow and metabolism during repeated asphyxias in newborn piglets: influence of theophylline. Biol Neonate 1994, 65:220-230.

128-GOVAERT P. Cranial haemorrhage in the term infant Mac Keith Press, 1993, 223 p.

129-GRAMELLINI D, FOLLI MC, RABONI S, VADORA E, MERIALDI A. Cerebral-umbilical ratio as a predictor of adverse perinatal outcome. Obstet Gynecol 1992, 79, 416-420.

130-GRAY PH, TUDEHOPE DI, MASEL JP, BURNS YR, MOHAY HA, O CALLAGHAN MJ, WILLIAMS GM.Perinatal hypoxic-ischaemic brain injury: prediction of outcome. Dev Med Chil Neurol 1993, 35, 965- 973.

131-GRAY PH, GRIFFIN EA, DRUMM JE, FITZGERALD DE, DUIGNAN NM. Continuous wave doppler   ultrasound in evaluation of cerebral blood flow in neonates. Archives of disease in childhood 1983, 58, 677-681.

132-GREEN RS, LEFFLER CW, BUSIJA DW, FLETCHER AM, BEASLEY DG. Indomethacin does not alter the circulating catecholamine response to asphyxia in the neonatal piglet. Pediatr Res 1987, 21:534-537.

133-GREISEN G.Methods for assessing cerebral blood flow.In : LEVENE MI, BENNETT MJ, PUNT J. (Editors):Fetal and neonatal neurology and neurosurgery, Churchill Livingstone 1988, 151-161.

134-GREISEN G, JOHANSEN K, ELLISON PH, FREDRIKSEN PS, MALI J, FRIIS-HANSEN B. Cerebral blood flow in the newborn infant : comparison of doppler ultrasound and 133   Xenon clearance. J Pediatr 1984, 104, 411-418.

135-GREISEN G, HELLSTROM-VESTAS L, LOUS H, ROSEN I, SVENNINGSEN N. Sleep-waking shits and cerebral blood flow in stable preterm infants. Peditr Res 1985, 19, 1156-1159.

136-GREISEN G. Ischaemia of the preterm brain. Biol Neonate 1992, 62, 243-247.

137-GREISEN G, TROJABORG W. Cerebral blood flow, Pa CO2 changes, and visual evoked potentials in mechanically ventilated, preterm infants. Acta Paediatr Scand 1987, 76, 394-400.

138-GREISEN G. Cerebral blood flow in preterm infants during the first week of life. Acta Paediatr Scand 1986, 75, 43-51.

139-GröNLIND JU, KERO P, KORVENRANTA H, AäRIMAA T, JALONEN J, TUOMINEN J, VäLIMAKI IAT. Cerebral circulation assessed by transcephalic electrical impedance during the first day of life- a potential predictor of outcome ? Early Hum Dev 1995, 41, 129-145.

140-GUNKEL JH, BANKS PLC. Surfactant therapy and intracranial hemorrhage: review of the literature and results of the analyses. Pediatrics 1993, 92:775-786.

141-GUYTON AC, HALL JE. Textbook of medical physiology. WB Saunders Company, 1996,1148 p.

142-HADDAD J, CHRISTMANN D, MESSER J (editors). Imaging techniques of the CNS of the

neonates. Springer- Verlag, 1991, 185 p.

143-HACKE W, HENNERICI M, GELMERS HJ, KRAMER G. Cerebral ischemia 1991, Springer-Verlag, 238p.

144-HAGEN-ANSERT SL (editor). Textbook of diagnostic ultrasonography (ed edition). CV Mosby, USA, 1983, 683 p.

145-HAMADA Y, HAYAKAWA T, HATTORI H, MIKAWA H. Inhibitor of nitric oxide synthesis reduces hypoxic- ischemic brain damage in the neonatal rat. Pediatr Res 1994, 35:10-14.

146-HAMILTON P, HOPE PL, CADY EB, DELPY DT, WYATT JS, REYNOLDS EOR. Impaired energy metabolism in brain of newborn infants with increased cerebral echodensities. Lancet 1986, 1, 1242-1246.

147-HAMMERMAN C, GLASER J, SCHIMMEL MS, FERBER B, KAPLAN M, EIDELMAN AI. Continuous versus multiple infusions of indomethacin: effects on cerebral blood flow velocity. Pediatrics 1995, 95, 244-248.

148-HANSEN NB, BRUBACK AM, BRATLID D, OH W, STONESTREET BS. The effects of variations in paCO2 on brain blood flow and cardiac output in the newborn piglet. Pediatr Res, 1984, 18, 1132-1136.

149-HANSEN NB, NOWICKI PT, MILLER RR, MALONE T, BICKERS RG, MENKE JA. Alterations in cerebral blood flow and oxygen consumption during prolonged hypocarbia. Pediatr Res 1986, 20, 147-150.

150-HANSEN NB, STONESTREET BS, ROSENKRANTZ TS, OH W. Validity of doppler measurements of anterior cerebral artery blood flow velocity : correlation with brain blood flow in piglets. Pediatrics 1983, 72, 526-531.

151-HARDERS A. Neurosurgical applications of transcranial Doppler sonography. Springer-Verlag, 1986, 134 p.

151b-HARRIS AP, HELOU S, TRAYSTMAN RJ, JONES MD, KOEHLER RC. Efficacy of the Cushing response in maintaining cerebral blood flow in premature and near-term fetal sheep. Pediatr res 1998,43:50-56.

152-HARTMANN A, KUSCHINSKY W (editors). Cerebral ischemia and calcium 1989, Springer-Verlag, 586p.

153-HAUGE A,THORESEN M, WALLE L. Changes in cerebral blood flow during hyperventilation and CO2- breathing measured   transcutaneously in humans by a bidirectional, pulsed, ultrasound doppler blood   velocitymeter. Acta Physiol Scand 1980, 110, 167-173.

154-HECHER K, SPERNOL R, STETTNER H, SZALAY S. Potential for diagnosing imminent risk to appropriate- and-small-for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow. Ultrasound Obstet Gynecol 1992, 2, 266-271.

155-HEISS WD, BEIL C, HERHOLZ K, PAWLIK G, WAGNER R, WIENHARD K. Atlas of position emission tomography of the brain. Springer Verlag 1985, 130p.

156-HEISS WD, GRAF R. The ischemic penumbra. Current Opinion Neurol 1994, 7:11-19.

157-HELLER S, WARD J. Neurologic consequences of hypoglycemia and pathogenic mechanisms involved in diabetic neuropathy. Current opinion in neurology and neurosurgery 1993, 6, 423-428.

158-HELLSTROM-WESTAS L, BELL AH, SVOK L, GREISEN G, SVENNINGESEN NW. Cerebroelectrical   depression following surfactant treatment in preterm neonates. Pediatrics 1992, 89, 643-647.

159-HENDRICKS SK, SORENSEN TK, WANG KY, BUSHNELL JM, SEGUIN EM, ZINGHEIM RW. Doppler   umbilical artery waveform indices- Normal values from fourteen to forty-two weeks. Am J Obstet Gynecol 1989, 161, 761-765.

160-HILL A. Current concepts of hypoxic-ischemic cerebral injury in the term newborn. Pediatr Neurol 1991, 7:317- 325.

161-IKEDA T, MORI N. Assessment of cerebral hemodynamics in pregnant women by internal carotid artery pulsed Doppler velocimetry. Am J Obstet Gynecol 1990, 163: 494-498.

161b-Ito U, KIRINO T, KUROIWA T, KLATZO I (editors). Maturation phenomenon in cerebral ischemia II. Springer, 1997,225 p.

162-IVACKO JA, SUN R, SILVERSTEIN FS. Hypoxic-ischemic brain injury induces an acute microglial reaction in perinatal rats. Pediatr Res 1996, 39, 39-47.

163-IWAMOTO HS, TEITEL D, RUDOLPH AM. Effects of birth-related events on blood flow distribution. Pediatr Res 1987, 22:634-640.

164-JACQZ-AIGRAIN E, WOOD C, ROBIEUX I. Pharmacokinetics of midazolam in critically ill neonates. Eur J Clin   Pharmacol 1990, 39:191-192.

165-JANOWSKI JS, FINLAY BL. The outcome of perinatal brain damage: the role of normal neuron loss and axon retraction. Dev Med Child Neurol 1986, 28, 375-389.

166-JESERICH G, ALTHAUS HH, WAEHNELDT TV. Cellular and molecular biology of .... NATO ASI Series H : vol 43, Springer Verlag, 1990, 565p.

167-JOBERT A, YOUNG AR, PETIT-TABOUE MC, TRAVERE JM, PAYEN D, MacKENZIE ET, BARON JC. Regional cerebral blood flow, blood volume, oxygen consumption and oxygen extraction fraction in etomidate- anaesthetized baboons studied by positron emission tomography. Circulation et Métabolisme du Cerveau 1995,   12, 217-213.

168-JOHNSON GL, BREART GL, GEWITZ MH, BRENNER JI, LANG P, DOOLEY KJ, ELLISON RC. Echocardiographic characteristics of premature infants with patent ductus arteriosus. Pediatrics 1983, 72, 864-871.

169-JORCH G, JORCH N. Failure of autoregulation of cerebral blood flow in neonates studied by pulsed Doppler ultrasound of the internal carotid artery. Eur J Pediatr 1987, 146, 468-472.

170-JORCH G, RABE H, GARBE M, MICHEL E, GORTNER L. Acute and protracted effects of intratracheal surfactant application on internal carotid   blood flow velocity, blood pressure and carbon dioxide tension in very low birth weight infants. Eur J Pediatr 1989, 148, 770-773.

171-JORCH G, MENGE U.Influence of pCO2 on brain perfusion in neonates - Doppler ultrasonography investigation. Monatsschi Kinderheilkd 1985, 133, 38-42.

172-JUGE O. Effets de l'hypoglycémie sévère sur le débit sanguin cérébral chez l'homme. Circulation et métabolisme du cerveau 1988, 5, 151-155.

173-KAMEI A, HOUDOU S, MITO T, KONOMI H, TAKASHIMA S. Developmental change in type VI collagen in human cerebral vessels. Pediatr Neurol 1992, 8, 183-186.

174-KANDA K, FLAIM SF. Effects of nimodipine in cerebral blood flow in conscious rat. J Pharmacol Exp Therapeutics 1986, 236, 41.

175-KEMPLEY ST, VYAS S, NICOLAIDES KH, GAMSU H. Cerebral and renal artery blood flow velocity before and after birth. Early Huma Dev 1996, 46, 165-174.

176-KIRKKINEN P, MULLER R, HUCH R, HUCH A. Blood flow velocity waveforms in human fetal intracranial arteries. Obstet Gynecol 1978, 70, 617-621.

177-KONTOS HA. Validity of cerebral arterial blood flow calculations from velocity measurements. Stroke 1989, 20, 1-3.

178-KOPELMAN AE. Blood pressure and cerebral ischaemia in very low birth wright infants.J Pediatr 1990, 116, 1000-1002.

179-KOYAMA K, MITO T, TAKASHIMA S, SUZUKI S. Effects of phenylephrine and dopamine on cerebral blood flow, blood volume, and oxygenation in young rabbits. Pediatr Neurol 1990, 6, 87-90.

180-KUBAN KCK, SKOUTELI H, CHERER A, BROWN E, LEVITON A, PAGANO M, ALLRED E, SULLIVAN KF. Hemorrhage, phenobarbital, and fluctuating cerebral blood flow velocity in the neonate. Pediatrics 1988, 82, 548-553.

181-KURMANAVICHIUS J, KARRER G, HEBISCH G, HUCH R, HUCH A. Fetal and preterm newborn cerebral blood flow velocity. Early Human Dev 1991, 26, 113-120.

182-LAPTOOK AR. The effect of sodium bicrabonate on brain blood flow and O2 delivery during hypoxemia and acidemia in the piglet. Pediatr Res 1985, 19:815-819.

183-LAPTOOK AR, ROSENFELD CR. Cerebral vascular responses to tolazoline infusions in the piglet. Early Human Dev 1985, 11:81-90.

184-LAPTOOK AR, CORBETT RJT, NGUYEN HT, PETERSON J, NUNNALLY RL. Alterations in cerebral blood flow and phophorylated metabolites in piglets after partial ischemia. Pediatr Res 1988, 23, 206-211.

185-LAPTOOK A, STONESTREET BS, OH W. The effects of different rates of plasmanate infusions upon brain blood flow after asphyxia and hypotension in newborn piglets. J Pediatr 1982, 100:791-796.

186-LAPTOOK AR, STONESTREET BS, OH W. Brain blood flow and O2 delivery during hemorrhagic hypotension in the piglet. Pediatr Res 1983, 17, 77-80.

187-LASSEN NA, SYMON L, BARON JC. Pénombre et ischémie cérébrale. John Libbey (London), 1986, 130p.

188-LAUDIGNON N, CHEMTOB S, BARD H, ARANDA JV. Effect of indomethacin on cerebral blood flow velocity of premature newborns. Biol Neonate 1988, 54, 254-262.

189-LAURIN J, LINGMAN G, MARSAL K, PERSSON PH. Fetal blood flow in pregnancies complicated by intrauterine growth retardation. Obstet Gynecol 1987, 69, 895-902.

190-LAWSON B, ANDAY E, GUILLET R, WAGERLE LC, CHANCE B, DELIVORIAPAPADOPOULOS M. Brain oxidative phosphorylation following alteration in head position in preterm and term neonates. Pediatr Res 1987, 22, 302-305.

191-LEES MH. Cardiac output determination in the neonate. J Pediatr 1983, 102, 709-711.

192-LEFFLER CW, BUSIJA DW, BEASLEY DG. Effect of therapeutic dose of indomethacin on the cerebral circulation of newborn pigs. Pediatr Res 1987, 21, 188-192.

193-LEFFLER CW, THOMPSON CC, ARMSTEAD WM, MIRRO R, SHIBATA M, BUSIJA DW. Superoxide scavengers do not prevent ischemia-induced alteration of cerebral vasodilation in piglets. Pediatr Res 1993, 33:164-170.

194-LEVENE MI, SHORTLAND D, GIBSON N, EVANS DH. Carbone dioxide reactivity of the cerebral circulation in extremely premature infants: effects of postnatal age and indomethacin. Pediatr Res 1988, 2, 175-179.

195-LEVENE MI, WILLIAMS JL, FAWER CL (editors). Ultrasound of the infant brain. SIMP, Oxford Blackwell Scientific Publications Ltd, 1985, 148 p.

196-LEVENE MI, LILFORD RJ, BENNETT MJ, PUNT J. Fetal and neonatal neurology and neurosurgery Churchill Livingstone 1995, 736p.

197-LEVENE MI, FENTON AC, EVANS DH, ARCHER LNJ, SHORTLAND DB, GIBSON NA. Severe birth asphyxia and abnormal cerebral blood flow velocity. Develop Med Child Neurol 1989, 31, 427-434.

198-LEVENE MI, GIBSON NE, FENTON AC, PAPATHOMA E, BARNETT D. The use of a calcium-channel blocker, nicardipine, for severely asphyxiated newborn infants. Develop Med Child Neurol 1990, 32, 567-574.

199-LEVITON A. Preterm birth and cerebral palsy : is tumor necrosis factor the missing link ? Develop Med Child Neurol 1993, 35, 553-558.

200-LEVY BI, PAYEN DM, TEDGUI A, XHAARD M, MCILROY MB. Non-invasive ultrasonic cardiac output measurement in intensive care unit. Ultrasound Med Biol 1985,11:841-849.

201-LEY D, MARSAL K. Doppler velocimetry in cerebral vessels of small for gestational age infants. Early Hum Dev 1992, 31, 171-189.

202-LINDNER W, SCHAUMBERGER M, VERSMOLD HT Ophtalmic artery blood flow velocity in healthy term and preterm neonates. Pediatr Res 1988, 24, 613-616.

203-LONGO LD, PEARCE WJ. Fetal and newborn cerebral vascular responses and adaptations to hypoxia. Seminars in Perinatalogy 1991, 15, 49-57.

204-LOU HC, LASSEN NA, FRIIS-HANSEN B. Decreased blood flow after administration of sodium bicrbonate in the distressed newborn infant. Acta Neurol Scand 1978, 57:239-247.

205-LOU HC, TWEED WA, DAVIES JM. Preferential blood flow increase to the brain stem in moderate neonatal asphyxia : reversal by naloxone. Eur J Pediatr 1985, 144, 225-227.

206-LOW JA. Cerebral perfusion, metabolism, and outcome. Cuurent Opinion Neurol 1995, 7 , 132-139.

207-LYNCH DR, DAWSON TM. Secondary mechanisms in neuronal trauma. Current Op Neurol 1994,

7, 510-516.

208-LYONS DT, VASTA F, VANNUCCI RC. Autoradiographic determination of regional cerebral blood flow in the immature rat. Pediatr res 1987, 21:471-476.

209-MADSEN JB, COLD GE (editors). The effects of anaesthetics upon cerebral circulation and metabolism. Springer-Verlag, 1990, 160 p.

210-MAERTZDORF WJ, TANGELDER GJ, SLAAF DW, BLANCO CE. Effects of partial plasma exchange transfusion on cerebral blood flow velocity in polycythaemic preterm, terms and small for date newborn infants. Eur J Pediatr 1989, 148, 774-778.

211-MARDOUM R, BEJAR R, MERRITT TA, BERRY C. Controlled study of the effects of indomethacine on cerebral blood flow velocities in newborn infants. J Pediatr 1991, 118, 112-115.

212-MARI G, DETER RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestationnal- age fetus. Am J Obstet Gynecol 1992, 166, 1262-1270.

213-MARI G, MOISE KJ, DETER RL, KIRSHON B, HUHTA JC, CARPENTER RJ, COTTON DB.Doppler assessment of the pulsatility index of the middle cerebral artery during cinstriction of the fetal ductus arteriosus after indomethacin therapy. Am J Obstet Gynecol 1989, 161, 1528-1531.

214-MARIE C, GEULDRY S, BRALET J. Effets du traitement par le pentobarbital sur le métabolisme ébergétique cérébral après réalisation d une ischémie complète et incomplète. Circulation et Métabolisme du cerveau 1986, 3:29-37.

215-MARTIN CG, HANSEN TN, GODDARD-FINEGOLD J, LEBLANC A, GIESLER ME, SMITH S. Prediction of brain blood flow using pulsed doppler ultrasonography in newborn lambs. J Clin Ultrasound 1990, 18, 487-495.

216-MARTIN CG, SNIDER AR, KATZ SM, PEABODY JL, BRADY JP. Abnormal cerebral blood flow patterns in preterm infants with large patent ductus arteriosus. J Pediatr 1982, 101, 587-593.

217-MARTINEZ A, PADBURY J, SHAMES L, EVANS C, HUMME J. Naloxone potentiates epinephrine release during hypoxia in fetal sheep : dose response and cardiovascular effects.Pediatr Res 1988, 23, 343-347.

218-MAULIK D. Hemodynamic interpretation of the arterial doppler waveforms.Ultrasound Obstet Gynecol 1993, 3, 219-227.

219-McCALL AL. The impact of diabetes on the CNS. Diabetes 1992, 4, 557-570.

220-McDONNELL M, IVES NK, HOPE PL. Intravenous aminophylline and cerebral blood flow in preterm infants. Arch Dis Child 1992, 67:416-418.

221-McGOWAN JE, MARRO PJ, MISHRA OP, DELIVORIA-PAPADOPOULOS M. Brain cell membrane function during hypoxia in hyperglycemic newbron piglets. Pediatr Res 1995, 37, 133-139.

222-McPHEE AJ, MAXWELL GM. The effect of Theophylline on regional cerebral blood flow responses to hypoxia in newborn piglets. Pediatr Res 1987, 21, 537-538.

223-MEADOW W, RUDINSKY B, BELL A, LOZON M, RANDLE C, HIPPS R. The role of prostaglandins and endothelium-derived relaxation factor in the regulation of cerebral blood flow and cerebral oxygen utilization in the piglet: operationalizing the concept of an essential circulation. Pediatr

Res 1994, 35:649-656.

223b-MEEK JH, TYSZCZUK L, ELWELL CE, WYATT JS. Cerebral blood flow increases over the first three days of life in extremely preterm neonates. Arch Dis Child Fetal Neonatal Ed 1998,78:F33-F37.

224-MEERMAN RJ, VAN BEL F, VAN ZWIETEN PHT, OEPKES D, DEN OUDEN L. Fetal and neonatal cerebral blood velocity in the normal fetus and neonates : a longitudinal doppler ultrasound study. Early Human Dev 1990, 24, 209-217.

225-MEISAMI E, TIMIRAS PS. Handbook of human growth and developmental biology.Volume I, part A. CRC Press, 1988, Florida USA, 200 p.

226-MELLANDER M, LARSSON LE. Effects of left-to-right ductus shunting on left ventricular output and cerebral blood flow velocity in 3-day-old preterm infants with and without severe lung disease. J Pediatr 1988, 113, 101- 109.

227- MENKE J, RABE H, BRESSER BW, GROHS B, SCHMITT RM, JORCH G. Simultaneous influence of blood pressure, pCO2, and pO2 on cerebral blood flow velocity in preterm infants of less than 33 weeks gestation.Pediatr Res 1993, 34, 173-177.

228 -MENKE J, MICHEL E, HILLEBRAND S, VON TWICKEL J, JORCH G. Cross-spectral analysis of cerebral autoregulation dynamics in high risk preterm infants during the perinatal period. Pediatr Res 1997, 42, 690-699.

229-MENT L, EHRENKRANZ RA, LANGE RC, ROTHSTEIN PT, DUNCAN CC. Alterations in cerebral blood flow in preterm infants with intraventricular hemorrhage. Pediatrics 1981, 68, 763-769.

230-MENT LR, DUNCAN CC, EHRENKRANZ RA, KLEINMAN CS, PITT BR, TAYLOR KJW, STEWART WB, GETTNER P. Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. J Pediatr 1985, 107:937-943.

231-MENT LR, EHRENKRANZ RA, DUNCAN CC. Intraventricular hemorrhage of the preterm neonate: prevention studies. Seminars in Perinatol 1988, 12:359-372.

232-MENT L, STEWART WB, PETROFF OAC, DUNCAN CC, MONTOYA D. Beagle puppy model of perinatal asphyxia : blockade of excitatory neurotransmitters. Pediatr Neurol 1989, 5, 281-286.

233-MERIC P. Etude par résonance magnétique nucléaire (RMN) in vivo du métabolisme cérébral. Circulation et Métabolisme du cerveau 1991, 8:53-70.

234-MESSER J, CASANOVA R. Transcranial Doppler evaluation of cerebral infarction in the neonate. Neuropediatrics 1991, 22, 147-151.

235-MIALL-ALLEN V, DE VRIES LS, DUBOWITZ LMS, WHITELAW A. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks gestation. Pediatrics 1989, 83, 657-661.

236-MICHENFELDER JD. Anesthesia and the brain. Churchill Livingstone, 1988, 215p.

237-MINNS RA. Problems of intracranial pressure du childhood.Clinics in Developmental Medicine 113/114, 1991, Mac Keith Press, 458p.

238-MIRRO R, ARMSTEAD W, BUSIJA D, GREEN R, LEFFLER C. Increasing ventilation pressure increase cortical subarachnoid cerebrospinal fluid prostanoids in newborn pigs.Pediatr Res 1987, 22,

647-650.

239-MIRRO R, LEFFLER CW, ARMSTEAD W, BEASLEY DG, BUSIJA DW. Indomethacin restricts cerebral blood flow during pressure ventilation of newborn pigs. Pediatr Res 1988, 24, 59-62.

240-MIRRO R, GONZALEZ A. Perinatal anterior cerebral artery doppler flow indexes : methods and preliminary results. Am J Obstet Gynecol 1987, 156, 1227-1231.

241-MIRRO R, LEFFLER CW, ARMSTEAD WM, GUSIJA DW. Pressure ventilation increases brain vascular prostacyclin production in newborn pigs. Pediatr Res 1990, 28:609-612.

242-MIRRO R, KARANTH S, ARMSTEAD WM, SHIBATA M, LEFFLER C. Alterations in cerebrovascular reactivity after positive pressure ventilation. Pediatr Res 1992, 32:114-117.

243-MITO T, KONOMI H, HOUDOU S, TAKASHIMA S. Immunohistochemical study of the vasculature in the developing brain. Pediatr Neurol 1991, 7, 18-22.

244-MOGILNER M, ASHWAL S, DALE PS, LONGO LD. Effect of nimodipine on newborn lamb cerebral blood flow. Biol Neonate 1988, 53, 279-289.

245-MOGILNER M, ASH WAL S, DALE PS, LONGO LD. Effect of nimodipine on newborn lamb cerebral blood flow. Biol Neonate 1988, 53, 279 - 289.

246-MONIN P, STONESTREET BS, OH W. Hyperventilation restores autoregulation of cerebral blood flow in postictal piglets. Pediatr Res 1991, 30, 294-298.

247-MOORTHY B, COLDITZ PR, IVES KN, REES DG, VAN'T HOFF WG, HOPE PL. Reproducibility of cerebral artery doppler measurements. Arch Dis Childh 1990, 65, 700-701.

248-MORRISON FK, HOWIE PW, MIRES GJ, HERD RM. Neonatal cerebral arterial flow velocity waveforms in term infants with and without metabolic acidosis at delivery. Early Hum Dev 1995, 42, 155-168.

249-MOUZINHO AI, ROSENFELD CR, RISSER R. Symptomatic patent ductus arteriosus in very-low-birth-weight infants: 1978-1989. Early Human Dev 1991, 27, 65-77.

250-MRAOVITCH S, SERCOMBE R (editors). Neurophysiological basis of cerebral blood flow control: an introduction, John Libbey, London, 1996, 408 p.

251-MULLAART RA, HOPMAN JCW, DE HAAN AFJ, ROTTEVEEL JJ, DANIELS O, STOELINGA GAB. Cerebral blood flow fluctuation in low-risk preterm newborns.Early Hum Dev 1992, 30, 41-48.

252-MURPHY DJ, HOPE PL, JOHNSON A. Neonatal risk factors for cerebral palsy in very preterm babies: case- control study. Br Med J 1997, 314, 404-408.

253-MYERS TF, PATRINOS ME, MURASKAS J, CALDWELL CC, LAMBERT GH, ANDERSON CL. Dynamic trend monitoring of cerebral blood flow velocity in newborn infants.J Pediatr 1987, 110, 611-616.

254-NEHLIG A. Effects of respiratory stimulants on cerebral metabolism and blood flow. Bilo Neonate 1994, 65:258- 264.

255b-NEWSHOLME EA, LEECH AR. Biochemistry for the medical sciences. John Wiley $ Sons,1983,952 p.

255-NICHOLLS JG, MARTIN AR, WALLACE BG (editors). From neuron to brain (a cellular and

molecular approach to the function of the neurons system), Third edition, Sinauer Associates Inc 1992, 807 p.

256-NIIJIMA S, SHORTLAND DB, LEVENE MI, EVANS DH. Transient hyperoxia and cerebral blood flow velocity in infants born prematurely and prematurely and at full term. Arch Dis Childh 1988, 63, 1126-1130.

257-OHLSON A, BOTTU J, GOVAN J, RYAN ML, FONG K, MYHR T. Effect of indomethacin on cerebral blood flow velocities in very low birth weight neonates with a patent ductus arteriosus. Dev Pharmacol Ther 1993, 20:100-106.

258-OHLSON A, BOTTU J, GOVAN J, RYAN ML, MYHR T, FONG K. The effect of dexamethasone on time averaged mean velocity in the middle cerebral artery in very low birth weight infants. Eur J Pediatr 1994, 153:363- 366.

259-OKUMURA A, HAYAKAWA F, KUNO K, WATANABE K. Periventricular leukomalacia and West syndrome. Dev Med Child Neurol 1996, 38, 13-18.

260-OMAR SY, GREISEN G, IBRAHIM MM, YOUSSEF AM, FRIIS-HANSEN B. Blood pressure responses to care procedures in ventilated preterm infants. Acta Paediatr Scand 1985, 74, 920-924.

261-OPPENHEIMER SM. Neurogenic cardiac effects of cerebrovascular disease. Current Opinion Neurol 1994, 7:20- 24.

262-OZEK E, KOROGLU TF, KARAKOC F, KILIC T, TANGOREN M, PAMIR N, BASARAN M, BEKIROGLU N. Transcranial Doppler assessment of cerebral blood flow velocity in term newborns. Eur J Pediatr 1995, 154, 60-63.

263-PADBURY JF, AGATA Y, POLK DA, WANG DL, CALLEGARI CC.Neonatal adaptation, naloxone increases the catecholamine surge at birth. Pediatr Res 1987, 21, 590-593.

264-PANETH N, RUDELLI R, KAZAM E, MONTE W. Brain damage in the preterm infant. (Clinics in Developmental Medicine No 131). Mac Keith Press, 1994, 209 p.

265-PAPE KE, WIGGLESWORTH JS. Haemorrhage, ischemia and the perinatal brain.SIMP William Heinemann,1979, 196p.

266-PASCHEN W, KOCHER M, HOSSMANN KA. Relationship between changes in putrescine and energy metabolites during early recirculation following ischemia of rat brain. Circulation et métabolisme du cerveau 1990, 7, 29-40.

267-PATEL J, MARKS K, ROBERTS I, AZZOPARDI D, EDWARDS AD. Measurement of cerebral blood flow in newborn infants using near infrared spectroscopy with indocyanine green. Pediatr Res 1998,43:34-39.

268-PEDEN CJ, RUTHERFORD MA, SARGENTONI J, COX IJ, BRYANT DJ, DUBOWITZ LMS .Proton spectroscopy of the neonatal brain following hyponic-ischaemic injury.Develop Med Child Neurol 1993, 35, 502- 510.

269-PELLICER A, CABANAS F, GARCIA-ALIX A, RODRIGUEZ JP, QUERO J. Natural history of ventricular dilatation in preterm infants : prognostic significance. Pediatr Neurol 1993, 9, 108-114.

270-PEREIRA de VASOCONCEVELOS A, COLIN C, BOYET S, NEHLIG A. Effets à court et à long terme d un traitement chronique précoce au phénobarbital sur la maturation du métabolisme énergétique cérébral et sur le comportement. Circulation et Métabolisme du cerveau 1989, 6:291-313.

271-PERLMAN JM, HILL A, VOLPE JJ. The effect of patent ductus arteriosus on flow velocity in the anterior cerebral arteries: ductal steal in the premature newborn infan. J Pediatr 1981, 99, 767-771.

272-PERLMAN JM, McMENAMIN JB, VOLPE JJ. Fluctuating blood-flow velocity in respiratory-distress syndrome. N Engl J Med 1983, 309, 204-209.

273-PERLMAN JM, ROLLINS NK, EVANS D. Neonatal stroke: clinical chracteristics and cerebral blood flow velocity measurements. Pediatr Neurol 1994, 11, 281-284.

274-PHILIPPON BL, CHERABIEH R, LAURENT B, SCHOTT B, BERGER M. Naloxone et débit sanguin cérébral dans la phase chronique des accidents ischémiques cérébraux. Circulation et Métabolisme du cerveau 1986, 3:39- 44.

275-PIATT JH, SCHIFF SJ. High dose barbiturate therapy in neurosurgery and intensive care. Neurosurgery 1984, 15:427-444.

276-PINARD E. Acétylcholine et circulation cérébrale.Circulation et Métabolisme du cerveau 1988, 5:172-182.

277-PIERRAT V, EKEN P, DE VRIES LS. The predictive value of cranial ultrasound and somatosensory evoked potentials after nerve stimulation for adverse neurological outcome in preterm infants. Dev Med Child Neurol 1997, 39, 398-403.

278-POURCYROUS M, LEFFLER CW, BADA HS, KORONES SB, STIDHAM GL, BUSIJA DW. Effects of pancuronium bromide on cerebral blood flow changes during seizures in newborn pigs. Pediatr Res 1992, 31:636- 639.

279-POURCYROUS M, LEFFLER CW, BADA HS, KORONES SB, STIDHAM GL, BUSIJA DW. Cerebral blood flow responses to indomethacin in awake newborn pigs. Pediatr Res 1994, 35:565-570.

280-PRECHTL HFR, EINSPIELER C, CIONI G, BOS AF, FERRARI F, SONTHEIMER D. An early marker for neurological deficits after perinatal lesions. Lancet 1997, 349, 1361-1363.

281-PRITCHARD JW, ALGER JR, BEHAR KL, PETROFF OAC, SCHULMAN RG. Cerebral metabolic studies in vivo by 31 P NMR. Proc Nath Acad Sci USA 1983, 80:2748-2751.

282-PRYDS O, GREISEN G, JOHANSEN KH. Indomethacin and cerebral blood flow in premature infants treated for patent ductus areriosus. Eur J Pediatr 1988, 147:315-316.

283-PRYDS O, GREISEN G, LOU H, FRIIS-HANSEN B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. J Pediatr 1989,115:638-645.

284-PRYDS O. Control of cerebral circulation in the high-risk neonate. Ann Neurol 1991, 30, 321-329.

285-PRYDS O, EDWARDS AD. Cerebral blood flow in the newborn. Archives Dis Child 1996, 74, F63-F69.

286-RAJU TNK, ZIKOS E. Regional cerebral blood flow velocity i infants. J Ultrasound Med 1978, 6, 497-507.

287-RAJU TNK. Cerebral doppler studies in the fetus and newborn infant. J Pediatr 1991, 119, 165-174.

288-RAJU TNK, KIM SY. The effect of hematocrit alterations on cerebral vascular CO_2 reactivity in newborn baboons. Pediatr Res 1991, 29, 385-390.

289-RAJU TNK. Some animal models for the study of perinatal asphyxia. Biol Neonate 1992, 62, 202-214.

290-RAJU TNK, DOSHI UV, VIDYASAGAR D. Cerebral perfusion pressure studies in healthy preterm and

newborn infants. J Pediatr, 1982, 100, 139-142.

291-RAJU TNK, KIM SY. Cerebral blood flow velocity acceleration and deceleration characteristics in newborn infants. Pediatr Res 1989, 26, 588-592.

292-RAMAEKERS VT, CASAER P, DANIELS H, MARCHAL G.The influence of blood transfusion on brain blood flow autoregulation among stable preterm infants. Early Human Dev 1992, 30, 211-220.

293-RAMSAY JM, MURPHY DJ, VICK III GW, COURTNEY JT, GARCIA-PRATS JA, HUHTA JC. Response of the patent ductus arteriosus to indomethacin treatment. Am J Dis Child 1987, 141, 294-297.

294-REED KL, ANDERSON CF, SHENKER L. Changes in intracardiac Doppler blood flow velocities in fetuses with absent umbilical diastolic flow. Am J Obstet Gynecol 1987, 157, 774-779.

295-RENNIE JM, SOUTH M, MORLEY CJ. Cerebral blood flow velocity variability in infants receiving assisted ventilation. Arch Dis Child 1987, 62, 1247-1251.

296-RENNIE JM. Cerebral blood flow velocity variability after cardiavascular support in premature babies. Arch Dis Child 1989, 64, 897-901.

297-RENNIE JM, LAM PKL. Effects of ethamsylate on cerebral blood flow velocity in premature babies. Arch Dis Child 1989, 64, 46-47.

298-RENNIE JM, DOYLE J, COOKE RWI. Ethamsylate reduces immunoreactive prostacyclin metabolite in low birthweight infants with respiratory distress syndrom. Early Human Dev 1986, 14, 239-244.

299-REUTER JH, DISNEY TA. Regional cerebral blood flow and cerebral metabolic rate of oxygen during hyperventilation in the newborn dog. Pediatr Res 1986, 20:1102-1106.

300-REUWER PJHM, SIJMONS EA, RIETMAN GW, VAN TIEL MWM, BRUINSE HW. Intrauterine growth retardation: prediction of perinatal distress by Doppler ultrasound. The Lancet 1987, 2, 415-418.

301-REY M, SEGERER H, KIESSLING C, OBLADEN M. Surfactant bolus instillation: effects of different doses on blood pressure and cerebral blood flow velocities. Biol Neonate 1994, 66, 16-21.

302-RIIKONEN RS, KERO PO, SIMELL OG. Excitatory amino acids in cerebrospinal fluid in neonatal asphyxia. Pediatr Neurol 1992, 8, 37-40.

303-RISBERG J, SMITH P. Prediction of hemispheric blood flow from carotid velocity measurements. A study with the doppler and 133 Xe inhalation techniques. Stroke 1980, 11, 399-402.

304-ROSENBERG AA, MURDAUGH E, WHITE CW.The role of oxygen free radicals in postasphyxic cerebral hypoperfusion in newborn lambs. Pediatr Res 1989, 26, 215-219.

305-ROSENBERG AA, NARAYANAN V, JONES MD. Comparison of anterior cerebral artery blood flow velocity and cerebral blood flow during hypoxia. Pediatr Res 1985, 19, 67-70.

306-ROSENBERG AA. Response of the cerebral circulation to hypocarbia in postasphyxia newborn lambs. Pediatr Res 1992, 32, 537-541.

307-ROSENKRANTZ TS, OH W. Cerebral blood flow velocity in infants with polycythemia and hyperviscosity: effects of partial exchange transfusion with plasmanate. J Pediatr 1982, 101, 94-98.

308-ROSENKRANTZ TS, OH W. Aminophylline reduces cerebral blood flow velocity in low-birth-weight infants. AJDC 1984, 138:489-491.

309-ROSENKRANTZ TS, PHILIPPS AF, SKRZYPCZAK PS, RAYE JR.Cerebral metabolism in the

newborn lamb with polycythemia. Pediatr Res 1988, 23, 329-333.

310-ROSENKRANTZ TS, STONESTREET BS, HANSEN NB, NOWICKI P, OH W. Cerebral blood flow in the newborn lamb with polycythemia and hyperviscosity. J Pediatr 1984, 104, 276-280.

311-ROSENKRANTZ TS, ZALNERAITIS EL. Prediction of survival in severely asphyxiated infants. Pediatr Neurol 1991, 7, 446-451.

312-ROOHEY T, RAJU TNR, MOUSTOGIANNIS AN. Animal models for the study of perinatal hypoxic-ischemic encephalopathy. Early Hum Dev 1997, 47, 115-146.

313-RUMACK CM, JOHNSON ML (editors). Perinatal and infant brain imaging. Year Book Medical Publishers, 1984, 248 p.

314-RUST RS. Energy of developing brain. Current Opinion Neurol 1994, 7, 160-165.

315-SABATINO G, QUARTULLI L, DI FABIO S, RAMENGHI LA. Hemodynamic effects of intravenous morphine infusion in ventilated preterm babies. Early Hum Dev 1997, 47, 263-270.

316-SALAMON G, RAYNAUD C, REGIS J, RUMEAU C (editors). Magnetic resonance imaging of the pediatric brain. An anatomical atlas. Raven Press, 1990, 350 p.

317-SALIBA EM, CHANTEPIE A, GOLD F, MARCHAND M, POURCELOT L, LAUGIER J Intraoperative measurements of cerebral haemodynamics during ductus arteriosus ligation in preterm infants. Eur J Pediatr 1991, 150, 362-365.

318-SALIBA E, AUTRET E, NASR C, SUC AL, LAUGIER J. Perinatal pharmacology and cerebral blood flow. Biol Neonate 1992, 62, 252-257.

319-SARNAT HB. Disturbances of late neuronal migrations in the perinatal period. Am J Dis Child 1987, 141, 969- 978.

320-SARNAT HB. Impairment of late neuroblast migration by ischemia. In: Lou HC, Greisen G, Larsen JF, (editors): Brain lesions in the newborn, Alfred Benzon Symposium, Munksgaard, Copenhagen 1994, pp 105-119.

321-SATOH S, KOYANAGI T, HARA K, SHIMOKAWA H, NAKANO H. Developmental charateristics of blood flow in the middle cerebral artery in the human fetus in utero, assessed using the linear-array pulsed Doppler method. Early Human Dev 1988, 17, 195-203.

322-SAUGSTAD OD.Hypoxanthine as an indicator of hypoxia : its role in health and disease through free radical production. Pediatr Res 1988, 23, 143-150.

323-SCALAIS E, BEHARRY K, PAPAGEORGIOU A, BUREAU M, ARANDA JV. Effects of phenobarbital on cerebral blood flow in the newborn piglet. Dev Pharmacol Ther 1992, 19:10-18.

324-SCALAIS E . Multimodality-evoked potentials in perinatal asphyxia. In : HADDAD J, SALIBA E (Eds) : Perinatal Asphyxia, 1993, Springer-Verlag, pp.147-165.

325-SCATTON B, CARTER C. Rôle des acides aminés excitateurs dans la pathohysiologie des dommages ischémiques cérébraux. Circulation et métabolisme du cerveau 1989, 6, 185-210.

326-SCHIPPER JA, MOHAMMAD GI, VAN STRAATEN HLM. The impact of surfactant therapy on cerebral and systemic circulation and lung function. Eur J Pediatr 1997, 156, 224-227.

327-SHAH N, LONG C, MARX W, DIRESTA GR, ARBIT E, MASCOTT C, MALLYA K, BEDFORD R.

Cerebrovascular response to CO2 in edematous brain during either fentanyl or isoflurane anesthesia. J Neurol Anesthesiol 1990, 2, 11-15.

328-SHORTLAND DB, GIBSON NA, LEVENE MI, ARCHER LNJ, EVANS DH, SHAW DE. Patent ductus arteriosus and cerebral circulation in preterm infants. Dev Med Child Neurol 1990, 32:386-393.

329-SCHRANZ D, STOPFLUCKEN H, SCHWARZ M, WALTHER B, ROCHEL M, JUNGST BK. Der einsatz von etomidat zur möglichen hirnprotektion. Monatsschr Kinderheilkd 1984, 132, 59-61.

330-SCHUMANN P, TOUZANI O, YOUNG AR, MacKENZIE ET. Effets de l indométacine sur le débit sanguin et le métabolisme oxydatif cérébral mesurés en tomographie par émission de positrons (TEP) chez le babouin anesthésié. Circulation et Métabolisme du Cerveau 1995,12, 270-271.

331-SEGAR JL, MERRILL DC, SMITH BA, ROBILLARD JE. Role of sympathetic activity in the generation of heart rate and arterial pressure variability in fetal sheep. Pediatr Res 1994, 35, 250-254.

332-SERI I, RUDAS G, BORS Z, KANYICSKA B, TULASSAY T. Effects of low-dose dopamine infusion on cardivascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates. Pediatr Res 1993, 34:742-749.

333-SHAH N, LONG C, MARX W, DIRESTA GR, ARBIT E, MASCOTT C, MALLYA K, BEDFORD R. Cerebrovascular response to CO2 in edematous brain during either Fentanyl or Isoflurane anesthesia. J Neurosurgical Anesthesiol 1990, 1:11-15.

334-SHAW PJ. Excitatory amino and receptors, excitotoxicity and the human nervous system. Current opinion in neurology and neurosurgery 1993, 6, 414-422.

335-SHORTLAND DB, GIBSON NA, LEVENE MI, ARCHER LNJ, EVANS DH, SHAW DE. Patent ductus arteriosus and cerebral circulation in preterm infants. Dev Med Child Neurol 1990, 32, 386-393.

336-SIESJO BK, WIELOCH T.Cellular and molecular mechanisms of ischemic brain damage.(Advances in neurology Vol 71), Lippincott-Raven , Philadelphia, 1996, 527 p.

337-SINGER HS, CHIU AY, MEIRI KF, MORELL P, NELSON PG, TENNEKOON G. Advances in understanding the development of the nervous system. Current Opinion Neurol 1994, 7, 153-159.

338-SIRRY HW, ANTHONY MY, WHITTLE MJ. Doppler assessment of the fetal and neonatal brain.In : LEVENE MI, BENNETT MJ, PUNT J. (Editors): Fetal and neonatal neurology and neurosurgery Churchill Livingstone 1988, 129- 144.

339-SIMONAZZI E, WLADIMIROFF JW, VAN EYCK J. Flow velocity waveforms in the fetal internal carotid artery relative to fetal blood gas and acid-base measurements in normal pregnancy. Early Huma Dev 1989, 19, 111-115.

340-SKOV L, PRYDS O, GREISEN G. Estimating cerebral blood flow in newborn infants: comparison of near infrared spectroscopy and 133 Xe clearance. Pediatr Res 1991, 30:570-573.

341-SKOV L, BELL A, GREISEN G. Surfactant administration and the cerebral circulation. Biol Neonate 1992, 61, Suppl 1, 31-36.

342-SNIDER AR. The use of doppler ultrasonography for the evaluation of cerebral artery flow patterns in infants with congenital heart disease. Ultrasound in Med and Biol 1985, 11, 503-514.

343-SONESSON SE, WINBERG P, LUNDELL BPW. Early postnatal changes in intracranial arterial blood

flow velocities in term infants. Pediatr Res 1987, 22, 461-464.

344-SONESSON SE, LUNDELL BPW, HERIN P. Changes in intracranial arterial blood flow velocities during surgical ligation of the patent ductus arteriosus. Acta Paediatr Scand 1986, 75, 36-42.

345-SONESSON SE, HERIN P. Intracranial arterial blood flow velocity and braibn blood flow during hypocarbia and hypercarbia in newborn lambs: a validation of range-gated Doppler ultrasound flow velocimetry. Pediatr Res 1988, 24, 423-426.

346-SONESSON SE, LUNDELL BPW, HERIN P. Changes in intracranial blood flow velocities during surgical ligation of the patent ductus arteriosus. Acta Paediatr Scand 1986, 75, 36-42.

347-SONESSON SE, HERIN. Intracranial arterial blood flow velocity and brain blood flow during hypocarbia and hypercarbia in newborn lambs, a validation of range-gated doppler ultrasound flow velocimetry. Pediatr Res 1988, 24, 423-426.

348-SPEER ME, BLIFELD C, RUDOLPH AJ, CHADDA P, HOLBEIN MEB, HITTNER HM. Intraventricular hemorrhage and vit E in the very low-birth-weight infant: evidence fir efficacy of early intramuscular vitamin E adminsitration. Pediatrics 1984, 74, 1107-1112.

349-STEIN DG, BRACHOWSKY S, WILL B (editors). Brain repair, Oxford University Press, 1995, 156 p.

350-STEWART WB. Blood flow and metabolism in the developing brain. Seminars in Perinatol 1987, 11:112-116.

350b-STEWARD P. Principles of cellular, molecular and developmental neuroscience. Springer Verlag, 1989, 257 p.

351-STIRIS T, SUGUIHARA C, HEHRE D, GOLDBERG RN, FLYNN J, BANCALARI E. Effect of cyclooxygenase inhibition on retinal and choroidal blood flow during hypercarbia in newborn piglets. Pediatr Res 1992, 31:127-130.

352-STIRIS TA, BLANCO D, COCOCEO R, LASA D, SUGUIHARA C, BANCALARI E, QUERO J. Effects of dexamethasone on retinal and choroidal blood flow during normoxia and hyperoxia in newborn piglets. Pediatr Res 1996, 40, 592-596.

353-STONESTREET BS, NOWICKI PT, HANSEN NB, PETIT R, OH W. Effect of aminophylline on brain blood flow in the newborn piglet. Dev Pharmacol Ther 1983, 6:248-258.

354-SVENNINGSEN NW, BLENNOW G, LINDROTH M, GADDLIN PO, AHLSTROM H. Brain-orientated intensive care treatment in severe neonatal asphyxia. Arch Dis Child 1982, 57, 176-183.

355-SHAW PJ. Excitatory amino acid receptors, excitotoxicity and the human nervous system. Current Opinion Neurol and Neurosurgery 1993, 6:414-422.

356-SYZMONOWICZ W, WALKER AM, YU VYH, STEWART ML, CANNATA J, CUSSEN L. Regional cerebral blood flow after hemorrhagic hypotension in the preterm, near-term and newborn lamb. Pediatr Res 1990, 28, 361-366.

357-TAYLOR GA. Alterations in regional cerebral blood flow in neonate stroke: preliminary findings with color Doppler sonography. Pediatr Radiol 1994, 24, 11-115.

358-TEGELER CH, BABIKIAN VL, GOMEZ CR (editors). Neurosonology. Mosby Year-Book, USA, 1996, 513 p.

359-TEITEL D, IWAMOTO H, RUDOLPH AM. Effects of birth-related events on central blood flow patterns. Pediatr Res 1987, 22, 557-566.

360-THIRINGER K, HRBEK A, KARLSSON K, ROSEN KG, KSELLMER I. Postasphyxial cerebral survival in newborn sheep after treatment with oxygen free radical scavengers and a calcium antagonist. Pediatr Res 1987, 22, 62-66.

361-THORESEN M, WHITELAW A. Effect of acetazolamide on cerebral blood flow velocity and CO_2 elimination in normotensive and hypertensive newborn piglets. Biol Neonate 1990, 58, 200-207.

362-TRAYNOR LA. Midazolam-Fentanyl sedation. Pediatrics 1991, 88:1286-1287.

363-TROMMER BL, GROOTHUIS DR, PASTERNAK JF. Quantitative analysis of cerebral vessels in the newborn puppy: the structure of germinal matrix vessels may predispose to hemorrhage. Pediatr Res 1987, 22, 23-28.

364-TWEED A, COTE J, LOU H, GREGORY G, WADE J. Impairement of cerebral blood flow autoregulation in the newborn lamb by hypoxia. Pediatr Res 1986, 20, 516-519.

365-VAN BEL F, VAN DE BOR M, BAAN J, RUYS JH. Cerebral blood flow velocity pattern in healthy and asphyxiated newborns: a controlled study. Eur J Pediatr 1987, 146, 461-467.

366-VAN BEL F, VAN DE BOR M, BAAN J, RUYS JH. The influence of abnormal blood gases on cerebral blood flow velocity in the preterm newborn. Neuropediatrics 1988, 19, 27-32.

367-VAN BEL F, HIRASING RA, GRIMBERG MTT. Can perinatal asphyxia cause cerebral edema and effect cerebral blood flow velocity ? Eur J Pediatr 1984, 142, 29-32.

368-VAN BEL F, DEN OUDEN L, VAN DE BOR M, STIJNEN T, BAAN J, RUYS JH. Cerebral blood-flow velocity during the first week of life of preterm infants and neurodevelopment at two years. Develop Med Child Neurol 1989, 31, 320-328.

369- VAN BEL F, KLAUTZ RJM, STEENDIJK P, SCHIPPER IB, TEITEL DF, BAAN J. The influence of indomethacin on the autoregulatory ability of the cerebral vascular bed in the newborn lamb. Pediatr Res 1993, 34, 178-181.

370-VAN BEL F, SOLA A, ROMAN C, RUDOLPH AM. Role of nitric oxide in the regulation of the cerebral circulation in the lamb fetus during normoxaemia and hypoxaemia. Biol Neonate 1995, 68, 200-210.

371-VAN DE BOR M, VAN DIJK JG, VAN BEL F, BROUWER OF, VAN SWEDEN B. Electrical brain activity in preterm infants at risk for intracranial hemorrhage. Acta Paediatr Scand 1994, 83, 588-595.

372-VAN DE BOR M, WALTHER FJ. Cerebral blood flow velocity regulation in preterm infants. Biol Neonate, 1991, 59, 329-335.

373-VAN DE BOR M, WALTHER FJ. Acceleration time in cerebral arteries of preterm and term infants. J Clin Ultrasound 1990, 18, 167-171.

374-VANNUCCI RC. Experimental biology of cerebral hyponic-ischemia : relation to perinatal brain damage. Pediatr Res 1990, 27, 317-326.

375-VANNUCCI RC. Perinatal metabolism. In:Polin RA, Fox WW (editors): Fetal and neonatal physiology, Vol 2,WB Saunders Company, 1992, 1510-1519.

376-VEILLE JC, KANAAN C. Duplex Doppler ultrasonographic evaluation of the fetal renal artery in

normal and abnormal fetuses. Am J Obstet Gynecol 1989, 161, 1502-1507.

377-VEILLE JC, COHEN I. Middle cerebral artery blood flow in normal and growth-retarded fetuses. Am J Obstet Gynecol 1990, 162, 391-396.

378-VEILLE JC, PENRY M. Effect of maternal administration of 3% dioxide on umbilical artery and fetal renal and middle cerebral artery Doppler waveforms. Am J Obstet Gynecol 1992, 167, 1668-1671.

379-VEILLE JC, HANSON R, TATUM K. Longitudinal quantitation of middle cerebral artery blood flow in normal human fetuses. Am J Obstet Gynecol 1993, 169, 1393-1398.

380-VERT P, MONIN P, SIBOUT M. Intracranial venous pressure in newborns : variations in physiologic state and in neurologic and respiratory disorders. In : Stern L, Friis-Hansen B, Kildeberg P (editors) : Intensive Care in the newborn. Masson Publishing USA, 1976, 185-196.

381-VOHR B, MENT LR. Intraventricular hemorrhage in the preterm infant. Early Human Dev 1996, 44, 1-16.

382-VOLPE JJ.Brain injury in the premature infant. Current concepts of pathogenesis and prevention. Biol Neonate 1992, 62, 231-242.

383-VOLPE JJ, PERLMAN JM, HILL A, Mc MENAMIN JP. Cerebal blood flow velocity in the human newborn : the value of its determination. Pediatrics 1982, 70, 147-152.

384-VOLPE JJ. Neurology of the newborns (3rd edition) 1995, WB Saunders Company,876 p.

385-WAGERLE LC, KUMAR SP, DELIVORIA-PAPADOPOULOS M. Effect of sympathetic nerve stimulation on cerebral blood flow in newborn piglets. Pediatr Res 1986, 20, 131-135.

386-WALLEN LD. Developmental physiology of the fetus and newborn and physiology changes related to birth, cerebral adaptation, and apnea. Current opinion in Pediatrics 1992, 4, 200-205.

387-WALTHER FJ, SIASSI B, RAMADAN NA, ANANDA AK, WU PYK. Pulsed Doppler determinations of cardiac output in neonates: normal standards for clinical use. Pediatrics 1985, 76:829-832.

388-WALTHER FJ, SIASSI B, RAMADAN NA, WU PYK. Cardiac output in newborn infants with transient myocardial dysfunction. J Pediatr 1985, 107, 781-785.

389-WALTHER FJ, SIASSI B, RAMADAN NA, WU PYK. Echocardiographic measurement of left ventricular stroke volume in newborn infants: a correlative study with pulsed Doppler and M-mode echocardiography. J Clin Ultrasound 1986, 14, 37-41.

390-WARDLAW SL, STARK RI, DANIEL S, FRANTZ AG. Effects of hypoxia on B-endorphin and B-lipoprotein release in fetal, newborn, and maternal sheep. Endocrinology 1981, 108, 1710-1715.

391-WARREN PS, GILL RW, GARRETT WJ. Doppler assessment of fetal blood flow, In : LEVENE MI, BENNETT MJ, PUNT J (editors): Fetal and neonatal neurology and neurosurgery Churchill Livingstone 1988, 169-173.

392-WATKINS AMC, WEST CR, COOKE RWI. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Human Dev 1989, 19, 103-110.

393-WEINDLING AM. Blood pressure monitoring in the newborn. Arch Dis Child 1989, 64, 444-447.

394-WEISGALS-KUPERUS N, BAERTS W, FETTER WPF, SAUER PJJ. Neonatal cerebral ultrasound, neonatal neurology and perinatal conditions as predictors of neurodevelopmental outcome in very low

birthweight   infants.Early Huma Dev 1992, 31, 131-148.

395-WELLS JT, MENT LR. Prevention of intraventricular hemorrhage in preterm infants. Early Hum Dev 1995, 42, 209-233.

396-WHYTE HE. Birth asphyxia, cerebral hemodynamic and cerebral lesions.Current Opinion in Pediatr 1992, 4, 217-227.

397-WIGGLESWORTH JS, SINGER DB (editors). Textbook of fetal and perinatal pathology, Blackwell Scientific Publications Ltd, 1991, Vol.1:640p, Vol. 2:1308 p.

398-WILCOX WD, CARRIGAN TA, DOOLEY KJ, GIDDENS DP, DYKES FD, LAZZARA A, RAY JL, AHMANN PA. Range-gated pulsed Doppler ultrasonographyc evaluation of carotid arterial blood flow in small preterm infants with patents ductus arteriosus. J Pediatr 1983, 102, 294-298.

399-WITHELAW A, DUBOWITZ L, PLACZEK M, LARY S. Phenobarbitone for prevention of periventricular haemorrhage in very low birth-weight infants. The Lancet 1983, 2:1168-1170.

400-WLADIMIROFF JW, HUISMAN TWA, STEWART PA. Intracerebral, aortic, and umbilical artery flow velocity waveforms in the late-first- trimester fetus. Am J Obstet Gynecol 1992, 166, 46-49.

401-WLADIMIROFF JW, VAN BEL F. Fetal and neonatal cerebral blood flow. Seminars Perinatol 1978, 11, 335-346.

402-WOO JK, LIANG ST, LO RSL, CHAN FY. Middle cerebral artery Doppler flow velocity waveforms. Obstet Gynecol 1978, 70, 613- 616.

403-WRIGHT LL, BAKER KR, HOLLANDER D, WRIGHT JN, NAGEY DA. Cerebral blood flow velocity in term newborn infants: changes associated with ductal flow. J Pediatr 1988, 112, 768-773.

404-WYATT JS, EDWARDS AD, AZZOPARDI D, REYNOLDS EOR. Magnetic resonance and near infrared spectroscopy for investigation of perinatal hypoxic-ischaemic brain injury. Arch Dis Child 1989, 64, 953-963.

405-WYATT JS, DELPY DT, COPE M, WRAY S, REYNOLDS EOR. Quantification of cerebral oxygenation and haemodynamic in sick newborn infants by near infrared spectroscopy. The Lancet 1986, 2:1063-1065.

406-YAGER JY, BRUCKLACHER RM, MUJSCE DJ, VANNUCCI RC. Cerebral oxydative metabolism during hypothermia and circulatory arrest in newborn dogs. Pediatr Res 1992, 32:547-552.

407-YASTER M, NICHOLS DG, DESHPANDE JK, WETZEL RC. Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. Pediatrics 1990, 86:463-467.

408-YOSHIDA H, YASUHARA A, KOBAYASHI Y. Transcranial doppler sonographic studies of cerebral blood flow velocity in neonates. Pediatr Neurol 1991, 7, 109-110.