Listening to the brain of the newborn by the Doppler Method

Dr Oreste Battisti, MD
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...”
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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 cognitive 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, auditory 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.

Acknowledgements.
I wish to incorporate many residents and colleagues for their collaboration in exchanging points of view and discussions, in participating in the handling aspects of that technique, and their criticism in this work.

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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):

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 described by the following formula:

\[ df = \frac{2FV \cos \alpha}{c} \]

where \( df \) = the frequency of Doppler shift;

\( F \) = the frequency of the emitted wave in MHz;

\( V \) = the velocity of the reflector;

\( \alpha \) = 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, \( C = 1540 \text{ - } 1560 \text{ m/s at } 37^\circ \text{ C.} \)

In 1880, Pierre and Marie Curie discovered the piezoelectric 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 ensure 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.
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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 0.5-1 dB/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:

\[
\text{Blood flow} = (\text{mean velocity}) \times 3.14 \times (\text{square root of vessel’s radius})
\]

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).
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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 occurring during the cardiac cycle.

Starting from the beginning 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 derived 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].
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* 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:

\[ R = \frac{(8 \, l \, n)}{r^4 \times 3.14} \]

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:

<table>
<thead>
<tr>
<th>AUC arbitrary units per min = (Hr b/min) x MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>or more precisely: AUC = (Hr b/min) x (1.113 MV + 1.566)</td>
</tr>
</tbody>
</table>

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:
  
  \[
  \text{MV in MCA / MV in Internal Carotid Artery (Normal range: 1.5-2).}
  \]

  The *intra-hemispheric* index of perfusion homogeneity also compares the area of perfusion of two arteries:

  \[
  \text{MV in MCA / MV in Anterior Cerebral Artery (normal range: 0.7-1.7).}
  \]

- the *inter-hemispheric* index of perfusion homogeneity compares one vessel in the left and in the right hemisphere:

  \[
  \text{MV in MCA one side / MV in MCA other side (normal range: 0.7-1.3).}
  \]

These indices can be useful to compare the perfusion areas of the ICA, the MCA and the ACA 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*
Table I.1. The anatomical approach of several arteries: technical aspects.

<table>
<thead>
<tr>
<th>Vessels</th>
<th>Windows</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior: ACA</td>
<td>- anterior fontanel, probe directed forward on parasagittal plane;</td>
</tr>
<tr>
<td></td>
<td>- angle &lt; 10°;</td>
</tr>
<tr>
<td></td>
<td>- quiet easy to pick up; difficult to differentiate left from right.</td>
</tr>
<tr>
<td>Middle: MCA</td>
<td>- parietal bone, just above the plane going from eyes to ears.</td>
</tr>
<tr>
<td></td>
<td>- very easy to pick up; ankle around 0°.</td>
</tr>
<tr>
<td>Artery</td>
<td>Access</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>basilar: BA</td>
<td>gap between the occipital bone and the atlas; difficult to pick up.</td>
</tr>
<tr>
<td>posterior: PCA</td>
<td>parietal bone;</td>
</tr>
<tr>
<td>vertebral: VA</td>
<td>through the neck;</td>
</tr>
<tr>
<td>Supratrochlear: STA</td>
<td>through the closed eyelids;</td>
</tr>
</tbody>
</table>

The anatomical approach of several arteries: illustrated approaches.
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 transducer 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 for 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);
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\[
PW = 0.5 \text{ age in days} + 24.5 \ (SD = 3) ; \\
= 1.1 \text{ post conceptional age in weeks} - 9.2; \\
- ACA by CW = 0.43 \text{ age in days} + 13 \ (SD = 3) ; \\
PW = 0.6 \text{ age in days} + 18.4 \ (SD = 3.7); \\
= 0.0698 \text{ age in hours} + 6.3;
\]

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

- \[ SV \text{ cm/sec} = 3.8 \text{ MV} - 3.06 \text{ DV} - 3.66; \]
- \[ DV \text{ cm/sec} = 1.24 \text{ MV} - 0.327 - 1.197; \]
- \[ MV \text{ cm/sec} = 0.81 \text{ DV} + 0.264 \text{ SV} + 0.97; \]

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

- RI is dependent on several factors:
\[
RI = 0.411 + 0.0192 \text{ pCO2 mmHg} + 0.00713 \text{ hematocrit %} + 0.0171 \text{ SV cm/sec} - 0.0572 \text{ MV} \ (r=0.775);
\]
- yet, we can describe a (lower) correlation with a single factor:
\[
RI = 1 - 0.0048 \text{ pCO2 mmHg} \ (r=0.55);
\]
\[
RI = 0.00571 \text{ age in days} + 0.638 \ (r=0.5);
\]
- 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 \text{ age in days} + 1.154 \ (SD = 0.15 ) ;
  \[ = 0.33 \text{ post-conceptional age in weeks} - 0.0061 \ (GA2) - 1.98. \]

**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:
- \( \text{AcT msec} = 0.149 - 0.00054 \text{ HR b/m} \), \( r = -0.984 \);
- \( \text{DcT msec} = 0.298 - 0.000107 \text{ HR b/m} \), \( r = 0.98 \).

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

\[ \text{AcT msec} = 1.3 \text{ post-conceptional age in weeks} - 12.7 \]

\[ \text{and} = 6 \text{ Body Weight in g} + 18.9. \]

In practice, it is better to use the ratio: \( \text{AcT/DcT} \). 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.**

<table>
<thead>
<tr>
<th>heart rate b/m</th>
<th>AcT msec</th>
<th>DcT msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>120</td>
<td>84</td>
<td>166</td>
</tr>
<tr>
<td>140</td>
<td>72</td>
<td>143</td>
</tr>
<tr>
<td>160</td>
<td>63</td>
<td>125</td>
</tr>
<tr>
<td>180</td>
<td>56</td>
<td>111</td>
</tr>
<tr>
<td>200</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

**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 \[\frac{\text{SBP mmHg}}{1.63 \text{ Sv cm/sec} + 21.3}\] between 0.54 - 1.46.
- the ratio \[\frac{\text{AUC-480}}{22.8 \text{ SV cm/sec} + 453}\] between 0.4 - 1.6.
- the RI between \[0.8-0.0363 \text{ pCO2 mmHg} - [1.2-0.0363 \text{ pCO2 mmHg}]\].
- the MV cm/sec between \[18-0.318 \text{ haematocrit } %\] - [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:
  
  \[\frac{\text{MV in MCA one side}}{\text{MV in MCA other side}}\]

- **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:
  
  \[\frac{\text{MV in MCA}}{\text{MV in ICA}} (\text{ranges: } 1.5-2);\]
  \[\frac{\text{MV in MCA/MV in ACA}}{\text{ranges: } 0.7-1.7};\]

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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:
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). |
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:

\[
CM g = \left(\frac{HC cm}{100}\right)^3 - \frac{1500}{HC cm}
\]

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:

\[
Cds = CBF \times aCs.
\]

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

<table>
<thead>
<tr>
<th></th>
<th>global tissue</th>
<th>grey matter</th>
<th>white matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO2</td>
<td>3.2</td>
<td>2.4</td>
<td>0.8</td>
</tr>
<tr>
<td>CMRG</td>
<td>5</td>
<td>3.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Molar ratio G/O2</td>
<td>1.38</td>
<td>1.1</td>
<td>1.17</td>
</tr>
</tbody>
</table>

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.
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 pCO2 or pO2, 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, pCO2 and pO2, the glucose and oxygen contents in arterial blood, and to the effects of several therapeutic agents.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DCBFV : in % or cm/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiac output (1)</td>
<td>1 cm SV / 8 ml</td>
</tr>
<tr>
<td>mean blood pressure (2)</td>
<td>1.5 cm SV/mmHg or 0.15 cm MV/mmHg</td>
</tr>
<tr>
<td>pCO2 (3)</td>
<td>3-4 % / mmHg</td>
</tr>
<tr>
<td>haematocrit (4)</td>
<td>0.35 cm MV/1%</td>
</tr>
</tbody>
</table>

(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 pCO2;

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 pCO2, 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.
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>
<thead>
<tr>
<th></th>
<th>In the white matter</th>
<th>In the grey matter</th>
<th>In global tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO2 in ml/100g/min: integrity</td>
<td>0.3</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>CMRO2: all functions</td>
<td>0.8</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>CMRG in ml/100g/min: integrity</td>
<td>0.7</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>CMRG: all functions</td>
<td>1.3</td>
<td>3.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

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 ( \( \% \ W \) ).

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

CBF or cerebral blood flow in \( \text{ml/100g/min} \); CBV or cerebral blood volume in \( \text{ml/100g} \). 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
36, O Battisti, Cerebral Doppler

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.

<table>
<thead>
<tr>
<th>Events</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>- decrease of CDO2,CDG;</td>
<td>- absence of CBF autoregulation within minutes.</td>
</tr>
<tr>
<td>- increase of CDCO2,CDH+;</td>
<td></td>
</tr>
<tr>
<td>- large release of excitatory aminoacids, cytokines, calcium, hydrogen, potassium, free radicals, nitric oxide, thromboxane, endothelin;</td>
<td>- blood brain barrier: leakage for small molecules (15 min) and after for large molecules (120 min);</td>
</tr>
<tr>
<td>- decrease of ATP;</td>
<td>- vasoconstriction (-&gt; 60 min); vasodilation (-&gt; 48 hrs);</td>
</tr>
<tr>
<td>- increase in numbers and sensitivity of receptors to EAA.</td>
<td>- blood flow redistribution: increase in cortex, decrease in WM.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- release of dopamine, adenosine, endorphins;</td>
<td>- 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.</td>
</tr>
<tr>
<td>- increase of antioxydants defenses, of neurotrophic synthesis, of astrocytes intervention, of synthesis of stress protein;</td>
<td>Regeneration or repair: Production of healing factors with an optimal level at about 10 days after insult.</td>
</tr>
<tr>
<td>- first decrease and further increase in synthesis of several proteins.</td>
<td></td>
</tr>
</tbody>
</table>
Gathered numbers of references (see details at the end of the book) in chapter II concerning the pathophysiology:

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.
- \[ CBF = 269.212 + 1.084 \text{ SBP} - 0.336 \text{ apCO}_2 \text{ mmHg} - 0.0072 \text{ apO}_2 \text{ mmHg} \]
41, O Battisti, Cerebral Doppler

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 pCO2:

- Cardiac output ml/kg/min = 7.6 SV cm/sec + 151 (r=0.98);
  \[= \frac{(AUC - 482)}{3.13} \text{ (r=0.73)};\]
  \[= 57 \text{ MV cm/sec} - 178 \text{ (r=0.672)};\]
- RI = 1.37 + 0.0015 SV cm/sec - 0.00648 pCO2 mmHg - 0.005 haematocrit % - 0.0087 MV cm/sec (r=0.726);
  \[= 1 - 0.0048 \text{ pCO2 mmHg} \text{ (r=0.597)};\]
- 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
Cerebral Doppler 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).
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.

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

* 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 knowledge).**

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+, CO2, O2, 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 rapidly sensitive to changes in pCO2 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 and Functions

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

### 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.

<table>
<thead>
<tr>
<th>Groups</th>
<th>CM/BW ratio in %</th>
<th>cardiac index L/m² body surface area</th>
<th>CBF/CO in %</th>
<th>CBF ml/100g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = RDS (n=441)</td>
<td>10.2 ± 0.8</td>
<td>2235 ± 1174</td>
<td>11.2 ± 5.95</td>
<td>5.5 ± 3</td>
</tr>
<tr>
<td>2 = CLD (n=72)</td>
<td>14 ± 6</td>
<td>2848 ± 285</td>
<td>22.6 ± 6</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>3 = Growth retarded (n=124)</td>
<td>14.6 ± 11</td>
<td>2891 ± 1611</td>
<td>21.4 ± 15.6</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>4 = Controls (n=132)</td>
<td>13.5 ± 0.9</td>
<td>3296 ± 1570</td>
<td>16.3 ± 7.7</td>
<td>13 ± 6</td>
</tr>
</tbody>
</table>

statistical comparison between groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>CM/BW ratio in %</th>
<th>cardiac index L/m² body surface area</th>
<th>CBF/CO in %</th>
<th>CBF ml/100g/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 and 3</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>1 and 4</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>2 and 3</td>
<td>Ns</td>
<td>Ns</td>
<td>&lt; 0.05</td>
<td>Ns</td>
</tr>
<tr>
<td>2 and 4</td>
<td>Ns</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>Ns</td>
</tr>
<tr>
<td>3 and 4</td>
<td>Ns</td>
<td>Ns</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
</tbody>
</table>

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:

\[(\frac{CBF}{CO})*100 = 1.05 \text{ GA weeks} - 18.3 \ (Sy = 5.2; \ r = 0.99)\]

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.

\[(\frac{CBF}{CO})*100 = 243 \ (CM/BW) - 14 \ (Sy = 5.2; \ r = 0.92)\]

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 conditions 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:

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
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;
- nitrotoprousside (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 care. 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:

\[
\text{mean BP torr} = 0.78 \text{ GA weeks} + 9 \quad [\text{sd} = 2.13, r=0.959].
\]

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>MBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 weeks</td>
<td>24-32</td>
</tr>
<tr>
<td>27</td>
<td>26-34</td>
</tr>
<tr>
<td>29</td>
<td>28-36</td>
</tr>
<tr>
<td>31</td>
<td>29-37</td>
</tr>
<tr>
<td>34</td>
<td>32-40</td>
</tr>
<tr>
<td>37</td>
<td>34-42</td>
</tr>
<tr>
<td>40</td>
<td>36-44</td>
</tr>
<tr>
<td>43</td>
<td>39-47</td>
</tr>
<tr>
<td>MBP torr equation</td>
<td>= 0.78 GA + 9 ( SD 2.13 )</td>
</tr>
</tbody>
</table>
55, O Battisti, Cerebral Doppler

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, these neonates have to be treated by colloids 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 colloids 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 colloidal 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 colloids and inotropic drugs infusion to treat early hypotension during RDS (median values in % from baseline).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Colloids infusion (n cycles = 675)</th>
<th>Inotropic drugs infusion (n cycles = 1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure: Systolic</td>
<td>+ 21</td>
<td>+ 11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+ 30</td>
<td>+ 28</td>
</tr>
<tr>
<td>Mean</td>
<td>+ 27</td>
<td>+ 17</td>
</tr>
<tr>
<td>CBV: mean</td>
<td>+ 70</td>
<td>+ 46</td>
</tr>
<tr>
<td>RI</td>
<td>- 8</td>
<td>- 15</td>
</tr>
<tr>
<td>Ac time</td>
<td>+ 37</td>
<td>+ 27</td>
</tr>
<tr>
<td>Dc time</td>
<td>+ 14</td>
<td>- 13</td>
</tr>
</tbody>
</table>

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 CO₂, 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 analysed 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%; EtCO₂= + 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 sickle babies.

In the next table, we summarize several items (states, drugs or manoeuvres) 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 mechanisms 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 wishing to have a look on cerebral circulation.

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

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 colloids (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:
CHAPTER V. The patency of the ductus arteriosus.

1. Assessment by Ultrasounds.


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 influence on 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.**

<table>
<thead>
<tr>
<th>Ratios</th>
<th>values for a significant PDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>[systemic / ductus] blood flow</td>
<td>&lt; 3.5</td>
</tr>
<tr>
<td>[Lventr / Aorta] diameter</td>
<td>&gt; 2.1</td>
</tr>
<tr>
<td>[L Atr / Ao] diameter</td>
<td>&gt; 1.4</td>
</tr>
<tr>
<td>[Rev / anter] AUC left carotid</td>
<td>&gt; 0.14</td>
</tr>
</tbody>
</table>

(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):

\[
\text{Qp/Qs} = 0.869 + 4.614 \times \text{R/A Lct} \quad (r = 0.988, \ p = 0.0002) \\
\text{DF ml/kg/min} = 32.3 + 553.7 \times \text{R/A Lct}
\]

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.

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

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 chosen 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.
Gathered numbers for the references (see details at the end of the book) for chapter V:

the patency of ductus arteriosus:

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 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 weight (and even more in cases of growth retardation). 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 undulations 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.

\[
\text{The ICP} = \text{Mean Arterial Pressure} - \text{Cerebral Perfusion Pressure} \\
\text{or} \\
\text{cerebral perfusion pressure} = \text{mean arterial pressure} - \text{ICP}
\]

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

\[
< \text{Invasive ICP mmHg} = 0.07 \text{ GA weeks} - 1.7 \text{ (SD=10%)}; r^2 = 0.82 .
\]

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.

\[
< \text{invasive MBP} = 0.78 \text{ GA} + 9 \text{ (SD=2.13)}. \\
< \text{invasive CPP} = 1.14 \text{ GA} - 2 \text{ (SD=15%); r}^2 = 0.95.
\]
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):

<table>
<thead>
<tr>
<th>GA weeks</th>
<th>ICP torr</th>
<th>CPP torr</th>
<th>MBP torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>&lt; 2</td>
<td>&gt; 20</td>
<td>&gt; 23</td>
</tr>
<tr>
<td>29</td>
<td>&lt; 2.4</td>
<td>&gt; 26</td>
<td>&gt; 29</td>
</tr>
<tr>
<td>32</td>
<td>&lt; 2.8</td>
<td>&gt; 30</td>
<td>&gt; 33</td>
</tr>
<tr>
<td>35</td>
<td>&lt; 3.4</td>
<td>&gt; 34</td>
<td>&gt; 38</td>
</tr>
<tr>
<td>38</td>
<td>&lt; 3.8</td>
<td>&gt; 38</td>
<td>&gt; 42</td>
</tr>
</tbody>
</table>

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 the 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 interhemispheric 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 Pourcelet 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 also 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:**

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

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

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

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,
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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 deprived 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 (traded by rhythmicity 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 surprising to observe in that situation a relative high cerebral/body mass ratio, and a variable degree of polycythemia, 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
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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;
- there 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 polycythaeemia.

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.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>318</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>49</td>
</tr>
<tr>
<td>Prolonged oxygen dependency</td>
<td>8</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>21</td>
</tr>
<tr>
<td>Intra- and peri-operative periods</td>
<td>34</td>
</tr>
<tr>
<td>Asphyxia or posthypoxic encephalopathy</td>
<td>23</td>
</tr>
<tr>
<td>Surfactant administration</td>
<td>12</td>
</tr>
<tr>
<td>Cerebral ventricular dilatation</td>
<td>14</td>
</tr>
<tr>
<td>Drugs for PDA, inotropics</td>
<td>35</td>
</tr>
</tbody>
</table>
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 delivery of a substrate (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)
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- 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 the quick index for the used formulas.

- The types of equipment
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 displayed.

- The practical aspects of the technique
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.

- The formulas (and the corresponding pages for description):
1. Christian Doppler formula (p 10);
2. Blood flow calculation (p 11);
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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 independency (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.

Appendix 6. Practice illustrated

- Anterior cerebral artery approach
• middle cerebral artery approach
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left carotid approach
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- superior mesenteric artery approach

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