A Practical Approach to Interpretation of CBF Measured by Mean of Xenon-CT in Patients with Traumatic Brain Injury

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Abstract: The measurement of cerebral blood flow (CBF) in traumatic brain injury (TBI) by means of Xenon-CT (Xe-CT) has been part of the clinical practice of several centres since 1980. Xe-CT consists of a CBF image coupled with CT which offers the possibility to associate morphologic features given by CT with functional information. Today, Xe-CT, in association with Positron Emission Tomography (PET), represents the gold standard for clinical quantitative measurement of CBF. More recently, Xe-CT has improved its potential application in the intensive care unit by means of portable CT scanner. The aim of the present review is to describe the practical experience of a single center with over five hundred Xe-CT studies obtained in more than two hundred TBI patients, to provide a method to guide the lecture of images at bedside, to present illustrative cases and to review the literature published so far on Xe-CT and TBI. The physiological and clinical variables which may be useful to explain global and regional CBF are detailed. Global CBF and its relationship with aging, the natural time course in TBI, and the dependency on physiological variables and therapy are discussed. The coupling of global CBF with cerebral metabolic rate of oxygen (CMRO2) and the relationship of arterial venous oxygen content differences (AVDO2) with patient outcome are analyzed. Finally, the current knowledge on regional CBF found in the most important traumatic lesions (posttraumatic cerebral infarction, contusion/laceration, acute subdural hematomas, and intraparenchymal hematoma) is described.

Keywords: Arteriovenous difference of oxygen, cerebral blood flow, cerebral metabolic rate of oxygen, ischemia, outcome, traumatic brain injury, Xenon CT.

INTRODUCTION

The measurement of cerebral blood flow (CBF) in traumatic brain injury (TBI) has always been an objective for clinicians. In fact, physiological data suggest that CBF drop may be associated with ischemia. Furthermore, most of the current therapies act on CBF by manipulating vessel resistance directly (e.g. PaCO2 and indomethacin), indirectly (e.g. mannitol), by means of coupling with metabolic depression (sedative, barbiturate, propofol, hypothermia), or by modifying the cerebral perfusion pressure (CPP), especially in cases with defective autoregulation.

However, technologies measuring CBF were not available for several years for every day clinical application. Xenon computed tomography (Xe-CT) consists of a CBF image coupled with CT which offers the possibility to associate morphologic features given by CT with functional information. It is a technique that has been available since the early eighties [1, 2]. Its application has often been limited by its location outside the intensive care unit (ICU) as well as by the not common immediacy of its measurement in relation to insults. More recently, the potential application of Xe-CT in ICUs has improved due to the introduction of a portable CT scanner [3]. It is now clear, however, that the measurement of CBF is not enough to understand the physiology of TBI and predict ischemia, at least when CBF measurement is performed outside the ICU [4]. Moreover, recent investigations have increasingly emphasized the relevance, after the early phases, of non-ischemic damage in TBI [5]. Once adequately treated in the first 24 hours and managed according to standard advanced NeuroICU care, most TBI patients seem to be affected prominently by a structural and metabolic disorder. In this context, CBF measurement should ideally be coupled with global and regional metabolic measurement. In particular, Xe-CT image should be co-registered with functional magnetic resonance imaging (fMRI) and with microdialysis or sensors of perfusion, PtO2 [6], thermal-diffusion measurement of regional CBF (TD-rCBF) [7,8] placed in selected brain regions. Xe-CT remains the most consistent alternative to positron emission tomography (PET) to quantitatively measure CBF. In fact, even if PET provides detailed physiological data [9], it is too complex to be widely applied. In spite of its limitations, Xe-CT, today, allows clinicians “to see” and “touch with their hand” what was merely speculatively imagined for a long time: the CBF. Consequently, the aim of this review was to describe a practical approach applied on a daily basis in a NeuroICU by performing Xe-CT measurements in a clinical setting currently consisting of standard monitoring of intracranial pressure (ICP), CPP, and jugular bulb saturation (SJ02).

What is Xenon-CT?

Xe-CT is an imaging technique that quantitatively measures CBF with a high spatial resolution (approximately 3-4...
mm). In 1945, Kety and Schmidt [10] introduced the nitrous oxide method for the quantitative measurement of CBF in humans. This pioneer technique was based on the Fick principle which states that the amount of a tracer in a tissue region is equal to the amount supplied by arterial blood minus the amount drained by venous blood. The same principle can be applied to stable the Xenon method, since the rate of uptake and clearance of an inert diffusible gas is proportional to blood flow in tissue. The agreement between the Kety Schmidt technique and Xe-CT was fairly good [11]. The reliability of Xe-CT has finally been established by means of comparison with radiolabelled microspheres methods [12,13].

Every CT scanner can be equipped for Xe-CT CBF imaging (Xe/TC system-2™, Diversified Diagnostic Products, Inc., Houston, TX). In our Department, CBF studies were conducted from 2000 to 2005 using a Picker 5000 CT scanner (Picker Medical Imaging, Cleveland, OH) and thereafter with a Philips Brilliance CT 6 slices Air Scanner (Philips International B.V., Amsterdam, The Netherlands). According to Pindzola and Yonas [14], wash–in protocol is performed using four contiguous axial sections separated by 20-mm intervals, located on the cerebral hemispheres, with the head aligned along the orbitomeatal plane. Two baseline scans separated by a time interval of 30 seconds are obtained at each of the four chosen levels. After a delay of 33 seconds and during approximately 4.5 minutes, six additional Xenon-enhanced scans are obtained at each level while the patient inhaled a mixture of 28% Xenon, 40% Oxygen and 32% room air. A reduction in Xenon concentration to 28% seemed appropriate to achieve an adequate signal-to-noise ratio for quantitative CBF measurement and to minimize flow activation [15]. During the two basal scans, the software records the Hounsfield value for each pixel. In the six additional Xenon-enhanced scans, the changes in Hounsfield values during the diffusion of the Xenon in the brain tissue are calculated. The difference between the baseline and the inhalation values (Fig. 1) is a function of the CBF values according to the Fick principle. The six enhanced scans are useful while waiting for the inhaled Xenon to reach an equilibrium with pulmonary arterial capillaries and to improve the accuracy of the final data through multiple measurements. The comparability of the values obtained by Xe-CT apparatus (from site to site and from scanner manufacturer to manufacturer) is possible by testing with phantom values [16].

The availability of an estimated value of arterial Xenon (Fig. 2) allows the quantitative calculation of CBF values. Several calculations are involved in the resolution of the CBF equation, derived from the Fick’s calculation. Among the variables affecting final CBF values, the most important is the hematocrit (Hct) which is used to convert the arterial concentration of Xenon \( Ca(t) = C_{max}(1- e^{-bt}) \) in CT Hounsfield units according to the equation: \( Ca(t) = C_{CT} * Xe(t) * (1+1.1Hct) \), where \( C_{CT} \) is the kVp dependent conversion constant, \( Xe(t) \) is end tidal Xenon measurement. Hematocrit measurement should be accurate, especially in acute unstable patients, because an inaccurately high Hct value is associated with the calculation of proportionally lower CBF values (Fig. 3).

**Specific Potential of Xenon-CT**

**Lambda:** Xenon is an ideal tracer for the measurement of CBF because it diffuses rapidly into the brain due to its high lipid content. This movement depends only on the volume of blood flow and the solubility of Xenon within the different tissue compartments of the brain. As lipid content is higher in white matter than in gray matter, solubility coefficient (lambda) is 1.4 in the former and 0.7 in the latter [17]. Xe-CT CBF is the only CBF technology that calculates lambda and integrates variations of this variable into the flow calculation. Therefore, this method most likely provides more accurate measurements than other quantitative CBF techniques even in disease conditions in which the lipid content could be altered. Fig. (4) shows differences in lambda occurring in apparently normal thalamus, in apparently normal frontal white matter and in a post-operative traumatic infarction.
Double tests: the rapid wash out of Xenon through alveolar ventilation ($t/2 \approx 30$ seconds) allows a fast clearance so that arterial Xenon concentration is less than $1\%$ after 5 minutes. This fast xenon clearance allows repeated tests within an interval as short as $10-20$ minutes from the baseline study.

**Limitations of Xenon-CT**

**Bone:** the partial volume effect related to bone may create artifacts, in particular, in basal frontal areas, (Fig. 5).

**Air:** A similar problem may be due to pneumoencephalus.

**Metal:** Artifacts due to metal affect Xe-CT more than CT image (Fig. 6). Care must be taken to remove any source of metal before the study.

**Motion:** Xe-CT studies in severe and moderate TBI patients who are artificially ventilated and sedated have potential advantages from immobilization. Movements on the part of the patient can affect the results of the study.

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**Fig. (2).** The wash-in phase. After the start of Xenon inhalation, along the upstream increase in airways Xenon concentration, the oscillation in the Xenon curve are due to the progressive improvement in the equilibrium between inhaled and exhaled (end tidal) Xenon concentration. The red points indicate the estimated arterial Xenon concentration.

**Fig. (3).** In patient with an hematocrit of $34\%$, we plotted the computation effect of simulated changes of Hct. An increase in hematocrit is associated with a decline in CBF.

**Fig. (4).** Figure shows differences in lambda (LAMB) in the exemplificative pixels located in high flow cortical region (left thalamus), in low flow area (right frontal white matter) and in a post surgical traumatic infarction.
of the patient may affect the alignment between the two baseline and the six inhalation scans. Consequently, motion mismatches the pixels among scans and the comparative calculation of the Hounsfield unit changes among the baseline pixel values toward inhalation pixel values (Fig. 7). An algorithm of the software (Xe-CT System Version 1.0 w ©, 1998, Diversified Diagnostic Products, Inc, Houston, TX) measures such phenomena and alerts the reader by introducing threshold values. Conventionally, a motion greater than 15% is considered to be unacceptable. At times in TBI patients, a passive mobilization occurs between the baseline and the six wash-in period and this error makes the study impossible to recover. Conversely, movement of restless patients during wash-in, can be, in part, corrected by the Xe-CT software, by excluding the moved scans only [18].

**Pulmonary mismatch**: Among the basic assumptions for CBF calculation is the fact that the arterial xenon concentration curve can be derived noninvasively from measurements of the xenon end-tidal concentration. Although this statement is accurate with normal pulmonary function, giving a rCBF discrepancy of only 0 ± 6% [19, 20], there is evidence of a significant divergence between end-tidal and arterial xenon concentrations in patients with TBI, who often have multiple causes of severe ventilation/perfusion ratio abnormalities. As a consequence, CBF can be underestimated on average by 18% when a 8-min wash-in, 8-min wash-out continuous xenon inhalation protocol is used [21]. A mismatch may be suspected if the slope to equilibrium between end tidal xenon and inhaled xenon is prolonged or the delta among the two values remains at plateau (Fig. 8).

**Transport**: In most hospitals CT scanners are not in the proximity of the ICU. It is well known that intra-hospital transport may be associated to secondary damage [22], which per se is a limitation for every extra ICU diagnosis. Modern centers currently include imaging units closely located to the ICU [23]. In patients with elevated ICP, who
could greatly benefit from functional CBF measurement, clinicians must balance the risk of transportation with the advantage expected from the study. Furthermore, in the specific case of CBF measurement, even the most appropriate and careful transportation is unlikely to maintain physiological stability as in NeuroICU so that related CBF changes should be expected, which affects the reliability of measurement.

**Radiation:** Radiation is a limitation of Xe-CT, however, estimation of biological consequences is difficult to evaluate. A study from Seifert [24] calculated that exposure may be associated with one case of fatal cancer out of 12,500 studies. This risk is relatively uncertain. A further study estimated that out of 100,000 patients examined over a period of 25 years, only 4 developed brain tumors [25]. In our department the CT-scanner is set to administer 120 kv and 150 mAs during the 32 slices of a Xe-CT study (8 basal slices and the 24 slices during the Xenon inhalation). The average surface dose per study is roughly of 400 mGy/cm.

**Flow activation:** Although biologically inert and, therefore, ideal for CBF measurements, xenon induces an uncoupling of brain function and metabolism [20], resulting in an increase in CBF. These findings have been accurately reviewed by Holl [26]. Analysis of the flow activation curve in humans with various intracranial insults showed a logarithmic shape [27]. An increase in TD-rCBF was observed be-
between 3% and 7% within the first 76 seconds of Xenon wash-in (12% after 190 seconds) while no further augmentation was detected until the end of the blood flow study [27]. A similar time course has recently been shown by Kim [28].

Fig. (9) illustrates a case in which flow activation is appreciable due to an error in the planning of scanning acquisition during the wash-in phase. All six acquisitions for the first basal skull level were acquired in rapid sequence, within seconds, followed after roughly 60 seconds by the next level. Owing to such imperfection, each level was acquired with a scheduled delay from each other. Consequently, as the basal slice was first acquired during the first minute after Xenon inhalation, it was the least flow activated, while, thereafter, the CBF increase seen in further levels was probably due to flow activation.

**White matter:** The low CBF in white matter prolongs the time needed to obtain an equilibrium between brain tissue and arterial xenon concentration. It has been estimated that more than 20 minutes are required to allow an accurate estimation of the lambda in white matter [29]. To reduce the risk of flow activation, however, the current wash-in phase lasts no longer than 4.5 minutes Xenon inhalation. Even if computational factor minimizes the relevance of such limitation on CBF calculation [14], the current method might underestimate rCBF values in white matter.

**Areas at low flow states:** Similarly to white matter, rCBF values might be underestimated in pathological areas affected by low flow values. These areas would be better evaluated with longer inhalation times [29].

**Potential Complications**

**Increase in ICP:** Xenon has an arterial vasodilatation effect, which is, in part, minimized by a low concentration (28%) and by a reduced time to exposition (4.5 minutes, in the wash-in protocol). Xenon-induced dilatation produces an increase in cerebral blood volume (CBV) that can potentially result in ICP elevation, depending on the state of cerebral compliance [26]. Clinical studies have shown minimal changes in ICP [30,31]. In our experience most instances of ICP increase were related to transport, the loss of head elevation [32] and the maneuvers directed to increase the minute ventilation required to compensate the dead space of the xenon enhancer. In a subset of 370 Xe-CT studies (unpublished data) performed in TBI patients with ICP monitoring, our data showed a statistically significant higher ICP levels measured at the end of the Xe-CT study in comparison with ICP values obtained before the xenon inhalation. However, this worsening of ICP values appeared to be only marginally relevant from a clinical point of view (Fig. 10).

**Fig. (10).** Intracranial pressure (ICP) measured in 370 Xe-CT studies, before xenon administration and at the end of the Xe-CT study. Grey rectangles represent the 95% confidence interval for comparing median values.

**Hypercapnia:** The 28% xenon mixture (with oxygen and nitrogen) is delivered by an enhancer which is connected to
the mechanical ventilator. This enhancer has an internal dead space which must be added to the baseline tidal volume (VT) set in the mechanical ventilator. During the initial phase of connection to the enhancer, EtCO₂ must be accurately checked, and should a value be above the baseline, VT has to be increased accordingly. The lower the initial VT, the more difficult it will be to find an appropriate setting. In such a context, pediatric patients deserve special attention. Inappropriate care or intrinsic difficulties in this phase may induce an acute increase in EtCO₂ and, subsequently, in ICP. At times, a decline in VT is associated to a decrease in pulse oxygen saturation.

Hypoxia: Patients with compromised pulmonary function requiring either a high level of pulmonary end expiratory pressure (≥ 10 cm H₂O) and/or FiO₂ values higher than 0.5, may encounter difficulties during the Xe-CT once connected to the enhancer [33]. Indeed, FiO₂ higher than 0.6 cannot be obtained due to the limiting effect in the gas mixture within the bag of the 28% xenon concentration.

When, Why and How an Xe-CT Study Should be Performed?

In terms of clinical practice, the nature of Xe-CT should be clear to the physician before attempting to use it. Is it a diagnostic tool, a physiological assessment, a monitoring modality or a test to dynamically evaluate the response to physiological or pharmacological challenges by means of repeated Xe-CT tests?

Xe-CT imaging is a snapshot in nature and, consequently, may be considered a diagnostic tool [34,35] which allows us to answer the question of whether a disease or a physiological derangement is present or not. Therefore, threshold values for ischemia (or hyperemia) should be selected and validated, with their positive and negative predictive values (PPV and NPV). Consequently, we can hypothesize that Xe-CT study may lead to the diagnosis of a specific derangement guiding us to choose the therapy required to revert it. Unfortunately, only few studies have cross evaluated CBF towards an in vivo gold standard of ischemia, which at the present can only be morphological. Von Oettlingen [36] showed that central low CBF areas in traumatic contusion evolve toward atrophy, but no cut-off value was evaluated. Similarly, no threshold values have been found for early global CBF when ventricle size (as a reflection of post-traumatic atrophy) is used as a late outcome measure of ischemia [37]. Most studies have assessed the relationship between ultra early (≤4 hours) low global CBF values below 20 ml/100gr/min and poor outcome [37], or the association between early post traumatic death and low CBF values, below 18ml/100gr/min [38]. More recently, a highly relevant paper by Cunningham [4] assessed CBF measurement (by means of PET, instead of Xe-CT) according to a probabilistic approach. The study showed that in TBI patients the PPV of threshold values for ischemia and penumbra is low. This result was confirmed by our team in patients with poor grade and complicated subarachnoid hemorrhage (SAH) due to a ruptured aneurysm, who were not selected for their a priori risk of post-procedural ischemia or vasospasm [39]. The most important cause of the poor PPV of CBF for ischemia is most likely to be the snapshot nature of Xe-CT. The time frame in which ischemia occurs is probably lost with episodic measurements. The second limitation of CBF measurements is represented by a reduction in oxygen metabolism developing independently after TBI [40,41] or in association with sedative-induced metabolic depression [42].

Considering hyperemia, our recent paper [44] showed an association between focal cortical hyperemia beneath an evacuated subdural hematoma (SDH) and unfavourable outcome, without definition of the predictive values of threshold levels of hyperemia toward focal atrophy at CT. Similarly, an association, but not a prediction, between global hyperemia and unfavourable outcome was established by Kelly [45,46].

So far, all these findings do not further support the categorization of Xe-CT within the range of diagnostic tools for TBI, but more likely suggest its potential as a physiological photography of global or regional derangements of CBF. While thresholds of ischemia as outcome prediction of a tissue have only probabilistic values, classical threshold values may still be useful in providing a simplified, standardized and comparable CBF interpretation. Low CBF values (as a proxy of a risk or actual ischemia) have been derived from laboratory studies on the baboon [47-49] and from human studies on stroke [50]. For hyperemia (an excessive CBF compared to actual needs), a CBF threshold of 55.3 ml/100gr/min has been derived from the normal CBF distribution [51]. Furthermore, in comatose patients, cerebral metabolic rate of oxygen (CMRO₂) is expected to be physiologically reduced and, consequently, a coupled reduction in CBF can be anticipated [52] with preservation of normal arteriovenous oxygen content difference (AVDO₂). According to Obrist [51], any excess in CBF, albeit within normal range, should be considered as a "relative" hyperemia (CBF >33.9 and <55.3), while values abnormally high, according to the Gaussian distribution of CBF, can be defined as "absolute hyperemia" [51]. Thresholds vary among the various authors. In this setting, to allow comparison with previous studies, rCBF values have been classified according to the following already reported thresholds values [49-51]: CBF<6 ml/100g/min (severe ischemia), CBF≥ 6 and <18
ml/100g/min (moderate ischemia), CBF ≥ 18 and <33.9 ml/100g/min (reduced flow), CBF ≥ 33.9 and <55.3 ml/100g/min (relative hyperemia) and CBF ≥ 55.3 ml/100g/min (absolute hyperemia).

A further potentially useful point of view is to look at Xe-CT as a monitoring tool. A snapshot imaging is not, by definition, a monitoring, which in critical care medicine is a continuous observation of a parameter. However, in a broader sense, repeated measurements of CBF by means of Xe-CT may give confirmation of the adequacy of management once adopted. For instance, at least three Xe-CT studies should be considered as an acceptable scheduled frequency of administration. Although this approach represented, until recently, the only possible approach to monitor CBF, after many years of pre-clinical application, the quantitative measurement of rCBF by means of TD-CBF [7] is now available as a real monitoring, albeit focal, at bedside. Even in consideration of all doubts concerning physiological thresholds, a further reason to measure CBF is to use it as a reference, comparing CBF after short perturbation of physiological variables, the so-called Xe-CT double test. These variables are normally used to evaluate meaningful responses to therapies. To our knowledge, only four kinds of tests have been applied by means of Xe-CT in TBI patients: induced hypocapnia [53-55], indomethacin bolus [56], norepinephrine-induced CPP elevation [57] and increase in FiO2 from 0.35 to 0.6 [6].

**Bias in Selection of Patients on Clinical Grounds**

As reported above, the patients who undergo Xe-CT are the result of a careful selection based on specific determinants. Since 2000 to date, only 234 out of 625 patients with severe TBI (37.4%), consecutively admitted to our NeuroICU, have undergone at least one Xe-CT study. Particularly, severe patients with abnormal pupil response and wide mass lesions are not often evaluated. This explains why only three series reported ultra early CBF measurement [38,58,59]. Consequently, patients at high risk of early global and focal ischemia and patients with refractory intracranial hypertension are often excluded, although CBF measurement may be more useful for them than in less severe patients. The reduced representation of patients with bilateral unreactive midriasis on admission (Fig. 11) and the high proportion of patients with better outcome among those who underwent Xe-CT confirm a case mix selection (Fig. 12).

**Physiological Findings During Xe-CT Study**

The interpretation of CBF values relies on the stability of physiological variables during the Xe-CT study. This is the specific objective of the physician, technicians or nurses under whose care the patients are placed. Furthermore, variables have to be recorded. The minimum mandatory set is: 1st PaCO2; 2nd mean arterial pressure; 3rd ICP, if available, and consequently CPP; 4th pulse oxygen saturation; 5th FiO2; 6th temperature; 7th Hb and Hct, the latter mandatory for CBF algorithm calculation. Furthermore, when a retrosgrade jugular catheter is inserted, simultaneous sampling of arterial and jugular bulb venous blood [60] for blood gas analysis and lactate and glucose measurements, is used to calculate the difference between arterial and venous contents of oxygen (AVDO2), and concentrations of glucose (AVDG) and lactate (AVDL). According to the Fick law, CMRO2, cerebral metabolic rate of glucose (CMRGl) and of lactate (CMRL) can be measured by multiplying the global CBF value, obtained after the Xe-CT study, for the corresponding arteriovenous differences.

**Different Outputs Format of Xe-CT Study**

After the performance of an Xe-CT study we have, at least, five types of potential outputs: 1st, a colored map of CBF for each of the four CT levels examined (Fig. 13); 2nd, quantitative analysis of data by means of single or multiple Region of Interests (ROI) wider than at least 8 x 8 x 10 mm3 (8 mm circle), to keep the error within 20% for flow in the range of 20 to 80 ml/100g/min (Fig. 14) [61]; 3rd, quantitative analysis according to the vascular territory (Fig. 15) [62]; 4th, pixels analysis of CBF according to selected thresholds (Fig. 16); 5th, free hand ROIs outlined on selected CT lesions (Fig. 17).

The colored map, due to the quantitative measurement of Xe-CT, corresponds to a continuous quantitative scale, but, obviously, visual perception makes it semi-quantitative. Data analysis requires a little more time and experience with the software. Consequently, at least in our Department, the physicians involved in the clinical field try to obtain functional indications more from semi-quantitative (colored maps) than quantitative analysis which is mainly restricted to research field. Such visual examination of CBF would allow us to move on different levels according to the interest that may focus mainly on either global or regional CBF. If the interest was directed to regional CBF, we would try to detect areas of low rCBF potentially leading to future brain damage. In this case, a low CBF should be considered as a risk factor, a potential cause of further damage (Fig. 18). Otherwise, we should focus our perspective more on the appearance of low rCBF when the lesion has already been established. In such a case, the rCBF more likely represents the effect of previous pathogenetic mechanisms leading to the lesion rather than the actual cause of the lesion itself. That is the case of hyperemia in low density region (Fig. 19). This finding is typical of lesions due to reversible compression or distortion of major artery territories. On the other hand, the rCBF measured in correlation with a CT lesion may be a cause of a further evolution of the lesioned areas (Fig. 20). For example low rCBF value in the periphery of a traumatic contusion can be implicated in a further extension of edema. In addition, regional CBF in a injured area may be useful as a proxy of tissue viability.
Important Factors Affecting Xe-CT Interpretation

Regardless of the selected output, CBF interpretation of a single study or repeated studies over days is affected by several factors, such as the natural history of disease, physiological changes in CBF or relevant variables, changes in management, etc. As all these variables are difficult to account for in a multivariate interpretation, this further reduces the chance of evaluating any causative effect of CBF, supporting a more practical use of CBF as a monitoring technique. However, at least four major findings always have to be considered: 1 - the difference in CBF levels in low and high flow areas such as gray and white matter contents; 2 - the influence of age on global CBF; 3 - the spontaneous time course of CBF; 4 - the effect of sedative therapies.

High and Low Flow Areas

In the original paper from Yonas [63], it is clearly described how the brain can be simplified into low and high
Fig. (15). The same Xe-CT study that in Figs. (13 and 14). The ROIs are now drawn according to main arterial vessels distribution, posterior cerebral artery, middle cerebral artery, anterior cerebral artery.

Fig. (16). The same Xe-CT study as in Figs. (13), (14) and (15). Pixels have been filtered according to a threshold value of CBF equal to 20 ml/100gr/min. Only pixels with CBF values below 20/ml/min are shown in CBF map and are superimposed on CT. The ratio of pixels below 20 ml/100gr/min compared to total pixels slices are described (9590/18002).

Fig. (17). The same Xe-CT study as in Figs. (13), (14), (15) and (16). Region of interest (ROI) drawn free hand on hypoattenuation areas.
Fig. (18). Panel at the top: patient with a reduction in rCBF in right hemisphere probably in association with regional intracranial hypertension. Panel at the bottom: the same patient after external decompression: the asymmetry of rCBF between the two hemispheres observed in the first Xe-CT study is no longer perceived. In such case the reduction in rCBF observed in the first Xe-CT was a potential cause of regional damage, while external decompression relieved regional hypoperfusion.

Fig. (19). Low attenuation in the area of the right middle cerebral artery due to a subacute sudural hematoma. After surgical removal, the hypoattenuation was found to be associated with hyperemia. In this case, hyperemia is probably an effect of a previous ischemia.
flow compartments. In fact, during analysis, the ROIs should be greater than 200 mm, to reduce the error of CBF measurement below 12% [16]. Consequently, the resolution of analysis is unable to discriminate between the cortical cortex and the underlying white matter. Areas with high flow are those with more gray matter: the cortical region, the thalamus and the basal ganglia. White matter, with the internal capsule is an area with low flow. The CBF in high and low flow compartments, sampled by placing 5-mm circular ROIs in regions containing the highest and lowest flow values in each hemisphere, averaged, in the original paper of Yonas [63], 84 ± 14 and 20 ± 5 ml/100gr/min, respectively [63]. These normative values should be kept in mind and compared with traditional values of ischemia threshold for the cortex which are 18 ml/100gr/min [49] and that for white matter, which should be at a much lower level (7 ml/100gr/min) [64].

The Influence of Age in Global CBF

Cerebral blood flow is deeply influenced by age, especially during the pediatric period [65]. On the basis of the paper by Suzuki [66] in unanesthetized, normal children, CBF may range from 40 ml/100gr/min during the first 6 months of life to 108 ml/100gr/min at 3 to 4 years of age, and then it decreases to 71 ml/100gr/min after 9 years of age [67]. After 19 years of age, CBF decreases gradually to adult levels. During ageing a further decline in CBF occurs [63], predominantly in the high flow compartment.

In TBI patients this association between ageing and reduction in CBF is depicted in Fig. (21), whereas raw values of global CBF per age are summarized in Fig. (22). The decline in CBF is probably a consequence of the physiological reduction in CMRO$_2$ [68] and CMRG. From a practical point of view, interpretation of Xe-CT in children should take into consideration that diffusely elevated rCBF values, specifically in cortical regions, are not automatically to be considered as pathological hyperemia. Consequently, interventions, e.g. indomethacin [69] or hyperventilation to control a physiological phenomenon are not justified. Furthermore, to our knowledge, age-adjusted CBF thresholds for ischemia are unknown, but they should be higher than in adults. Consequently, apparently adequate and decreased CBF values in children should be evaluated with caution.

Conversely, markedly reduced CBF values in elderly patients [70] must not automatically be considered as a risk for ischemia, but, for example, the relevance of added sedation should be taken into account. This latter aspect is particularly relevant when considering that the aged brain is more sensitive to the depressive effect of sedation, if the dose is not adjusted for age [71].

Time Course of CBF

Several studies have evaluated the time course of CBF after injury and converging findings suggest that, in the first hours post injury (phase 1), global CBF is markedly reduced, increases then during days 2-4 (phase 2) and thereafter decreases toward levels higher than those observed in the first 24 hours (phase 3), both in adults [72-76] and in children [77,78]. Fig. (23) describes the time course of global CBF in 522 studies (unpublished data). A similar time course of rCBF has been observed in traumatic contusion by means of intravenous $^{133}$Xenon [79], in traumatic intra-parenchymal hematoma [75] and in the cortex below the evacuated SDH by means of Xe-CT [44]. Although this pattern has been described in pooled patients with TBI it seems to characterize only patients with unfavorable outcome as shown in two

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Fig. (20). rCBF decrease below a traumatic hematoma is associated to a worsening of hypoattenuation in the next Xe-CT study. The further reduction in rCBF is the cause of further damage.
studies in which data were dichotomized for favourable and unfavourable outcome [44, 76]. According to these studies, this pattern proved to apply to both global CBF [76] and regional CBF, at least in patients affected by isolated SDH [44].

Interpretation of the CBF time course is not yet clear, and several different factors may interact at the different phases of the time course. Indeed, initial CBF depression (phase 1, oligoemic-ischemic) may represent the result of several effects. First, the reason for early oligemia could be merely computational as all studies included patients who died early and in whom very low CBF values and irreversible ischemia were established [38,59]. Consequently, these patients, by self exclusion, did not contribute to the more elevated levels of CBF observed in phase 2. Second, immediately after trauma a non ischemic decline in CMRO₂, coupled with subsequent CBF decrease, occurs as a result of physiological changes after the initial impact [80-83]. Third, several factors may contribute to true global, multifocal or regional hypoperfusion, without an association with an irreversible outcome. Recently, a study by the Robertson group [58] showed that an early reduction in global CBF is predominantly associated to elevated ICP levels and reduced CPP values. The hypothesis that low CBF values should be due to ischemia was also supported by PET studies [84, 85]. Consequently, today, it would seem that early low CBF values

**Fig. (21).** Illustrative cases showing the decline in CBF with ageing.

**Fig. (22).** Box plot showing median and interquartile ranges of global CBF according to age. Data from 500 Xe-CT studies (unpublished data).
below 18 ml/100gr/min could be a red flag for true ischemia. Similarly to phase I, phase 2 (hyperemic) may, in part due, be to the exclusion of patients with very low CBF who died and were not further observed. More probably, however, hyperemia represents a state of uncoupling between CMRO$_2$ and CBF in favor of a coupling between CMRG and CBF [86]. An increase in CMRG is probably due to enhancement of glycolysis which is useful in reparative processes. Assuming that higher repair needs are associated with more severe initial damage, more hyperglycolysis can be expected, resulting in worsening of CMRO$_2$/CBF uncoupling. Enhanced CMRO$_2$/CBF uncoupling may, in turn, explain the association between unfavourable outcomes and global [76], as well as regional, [44] hyperemia. The third phase, with a reduc-

The Effect of Sedative Therapies

Cerebral blood flow is coupled to CMRO$_2$ which, in turn, is coupled to neuronal activity [40]. Sedatives and anesthetics may reduce CBF by depressing neuronal activity and consequently CMRO$_2$ and CMRG [87]. Infusion with barbiturate [42] or propofol [88, 89] and high doses of benzodiazepine can reduce CBF in a substantially coupled manner. Sedation is applied in most patients so that its impact on CBF cannot be isolated. However, once barbiturate and propofol are added to control refractory intracranial hypertension, a significant CBF depression can occur as shown in Fig. (24). Summary data confirm lower median CBF values in patients with continuous barbiturate infusion (Fig. 25). The reduction in CBF due to sedatives interferes with the interpretation of decreased CBF due, primarily, to low CPP [58] or to the trauma itself [41, 52, 83]. In fact, CMRO$_2$ is naturally reduced after TBI [40, 41, 82]. The clear relationship between CMRO$_2$ and GCS [40, 51, 76] suggests that CMRO$_2$ is naturally related to initial trauma severity. Data from our observations show, as expected, no association between best GCS before ICU admission and CBF (Fig. 26, results from 505 Xe-CT studies, unpublished data). However, from the same data only a slight association between reduced CMRO$_2$ and the best GCS was found (Fig. 27, results from 393 Xe-CT studies, unpublished data), most likely owing to the practice to sedate patients with benzodiazepine and opioids [90,91], and the fact GCS is less reliable in the actual initial care context [92, 93]. All these findings may even explain why it is so difficult to find clear CBF thresholds for the prediction of ischemia [4]. Hypothermia is a further depressor of CBF that should be borne in mind during CBF interpretation (Fig. 28) [94].

Fig. (23). Time course of global CBF in 522 Xe-CT studies (unpublished data). Grey rectangles represent the 95% confidence interval for comparing median values.

Fig. (24). A young adult patient with severe TBI and refractory intracranial hypertension. The more elevated baseline CBF was obtained during deep continuous sedation with benzodiazepine and fentanyl. However the day after, due to a progressive increase in ICP, continuous barbiturate infusion was added to previous sedation plane. The correspondent depressed global CBF should be the consequence of the barbiturate induced decline in cerebral metabolic rate of oxygen.

Fig. (25). Median global CBF values are lower in Xe-CT studies obtained during barbiturate infusion. Data from 522 Xe-CT studies (unpublished data) Grey rectangles represent the 95% confidence interval for comparing median values.
Quantitative Interpretation of Global CBF

Normal CBF values are a statistic concept more than a biological one. In TBI patients, a normal (Gaussian) distribution of CBF is expected and consequently “normal” values may be derived. Considering only patients between 15 and 65 years (448 Xe-CT studies, unpublished data), we found a mean CBF value of 40.0 ± 15.7 ml/100gr/min (Fig. 29). Such CBF values do not seem to be different from those reported by Glenn et al. (40.2 ± 13.2 ml/100gr/min) which were lower than those measured in normal volunteers in the same institution (46.2 ± 10.5 ml/100gr/min) using the intravenous $^{133}$Xenon clearance technique [82]. One way of interpreting CBF is to try to understand, by means of a multiple regression analysis, the several variables which affect CBF (Table 1). In a series of 423 studies, age, Xe-CT measurements within 24 hrs post injury, hematocrit, barbiturates and ICP negatively correlated with global CBF values which positively correlated with PaCO$_2$ values. Surprisingly, CBF did not correlate with CPP (Fig. 30), as previously reported in a smaller series [95] and confirmed by others [55, 96, 97]. These findings may be accounted for in various ways. The

Fig. (26). No association has been found between the best Glasgow Coma Scale score (GCS) values observed the first day post injury and CBF values. Data from 505 Xe-CT studies (unpublished data). Grey rectangles represent the 95% confidence interval for comparing median values.

Fig. (27). A slight association has been found among best Glasgow Coma Scale score (GCS) values observed the first day post injury and lower cerebral metabolic rate of oxygen (CMRO$_2$) values. Data from 393 Xe-CT studies (unpublished data). Grey rectangles represent the 95% confidence interval for comparing median values.

Fig. (28). Reduced median global CBF values Xe-CT studies during hypothermia. Data from 546 Xe-CT studies (unpublished data) obtained in patients managed with core temperature below 34 °C. Grey rectangles represent the 95% confidence interval for comparing median values.
The multiple regression shown in Table 2 can be improved in its prediction to 41% by adding AVDO₂ to variables (377 Xe-CT studies, unpublished data). However, we can consider that AVDO₂ values depend on CBF and CMRO₂ levels, and not vice-versa [98]. In spite of this, AVDO₂ remains of interest as an estimate of global CBF.

The main reason might be that most patients are physiologically located in the middle of the autoregulatory curve so that CBF, once ICP and mean arterial pressure (MAP) have been adequately managed, depends more on trauma severity and CMRO₂ rather than on systemic variables, at least in selected patients. Such results are affected by case mix selection and the time frame in which the CPP and CBF relationship is observed. In fact, as shown by Hlatky et al. [58], a remarkable relationship between CPP and CBF was shown in the early phases post injury, most likely as a result of the predominance of patients with low CPP values and deranged autoregulation.
(Fig. 31), with a correlation factor similar to that obtained with a combination of multiple variables such as age, measurements within 24 hrs post injury, hct, barbiturate, ICP and PaCO2 values (Table 1). It seems, therefore that basic clinical information can only partially explain and predict global CBF values, suggesting that additional variables should be investigated, although our potential to understand global CBF is still limited. Further, while only barbiturates seem to affect CBF in multivariate analysis, it is unclear, however, whether increasing the dosage would result in further CBF reduction [95, 99]. In fact, such a hypothesis is not supported by our data showing that CBF is not significantly lower in more intensely treated patients, which may be a consequence of uncoupling from oxygen metabolism (Fig. 32). Conversely, CMRO2 is reduced in Xe-CT studies performed in patients in extreme therapy for refractory intracranial hypertension (Fig. 33). However, in the interpretation of data it has to be remembered that deeper sedation delivered over a longer period is commonly used in more severe patients with higher ICP levels. Since severity is intrinsically associated with lower CMRO2 values [40], lower CMRO2 in these patients could be fundamentally cross linked to a treatment associated CMRO2 depression.

Physiological variables may contribute to the definition of trauma outcome. It is well established that low global CBF values have some relation to early death [38,59] and with an unfavorable outcome [59, 76] only in the first hours post injury. In our population (Fig. 34), patients who died had reduced CBF values. One of the reasons explaining why, overall, CBF is a poor predictor of outcome is that after the first 24 hours uncoupling predominates, as shown by the increase in AVDO2 [80]. The reasons why CBF is uncoupled

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Table 1. Variables predictive of the global CBF in 423 Xe-CT studies in severe and moderate TBI patients ventilated and sedated (unpublished data). This model explains 30.4% of the global CBF values.

<table>
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<th>Variable</th>
<th>Coefficient</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>53.4909</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.247933</td>
<td>≤ 0.0001</td>
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<tr>
<td>Measurement within 24 hr post injury</td>
<td>-4.40421</td>
<td>0.0479</td>
</tr>
<tr>
<td>Htc (%)</td>
<td>-1.1577</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>0.83723</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>ICP mean (mmHg)</td>
<td>-0.101575</td>
<td>0.0881</td>
</tr>
<tr>
<td>Continuous barbiturate infusion</td>
<td>-6.97103</td>
<td>0.0414</td>
</tr>
</tbody>
</table>

ICP mean: the mean hourly intracranial pressure (ICP) measured the same day of Xe-CT study.

barbiturate: continuous infusion of barbiturate in association with benzodiazepine (day of the study).

Table 2. Variables predictive, including Arterial-Venous O2 content difference (AVDO2), of the global CBF in 377 Xe-CT studies in severe and moderate TBI patients ventilated and sedated (unpublished data). This model explains 41.2% of the global CBF values.

<table>
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<th>Variable</th>
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<tbody>
<tr>
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<tr>
<td>Age (years)</td>
<td>-0.179419</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>-0.557251</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>ICP mean (mmHg)</td>
<td>-0.113539</td>
<td>0.0435</td>
</tr>
<tr>
<td>Continuous barbiturate infusion</td>
<td>-9.66229</td>
<td>0.0030</td>
</tr>
<tr>
<td>Continuous propofol infusion</td>
<td>-2.66441</td>
<td>0.0377</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>0.229551</td>
<td>0.0729</td>
</tr>
<tr>
<td>AVDO2 (ml/dl)</td>
<td>-4.88004</td>
<td>≤ 0.0001</td>
</tr>
</tbody>
</table>

ICP mean: the mean hourly intracranial pressure (ICP) measured the same day of Xe-CT study.

Continuous barbiturate infusion: continuous infusion of barbiturate in association with benzodiazepine and fentanyl (day of the study).

Continuous propofol infusion: continuous infusion of propofol in association with benzodiazepine and fentanyl (day of the study).
from metabolism are complex and might involve disturbance in autoregulation, early ischemia with elevated oxygen extraction, irreversible ischemia with defective oxygen extraction, hypometabolism or coupling with glucose rather than oxygen. While CBF is poorly informative regarding outcome, through global CBF measurement it is possible to calculate global CMRO₂, which has been found to be reduced in TBI in several studies [40]. Patients with better Glasgow Outcome Scale [100] at one year are associated with wider AVDO₂ (Fig. 35) and higher CMRO₂ values (Fig. 36). These results seem to complete the observation coming from Stocchetti et al., who demonstrated that wider AVDO₂ values are associated with improved outcomes [101].

**Bedside Interpretation of Global CBF Values**

Bearing in mind all the aforementioned considerations, we can now attempt to describe an oversimplified approach based on low and high global CBF values. Even if the visual perception may be different from the quantitative one, for instance, we can consider low CBF values as those below 18 ml/100gr/min and high CBF values as those above 33 ml/100gr/min [49-51]. Global low CBF is one of the most difficult findings to interpret. In fact, ageing, the severity of trauma and deep sedation with metabolic suppressive drugs may affect CBF
with a coupled reduction, without ischemic decline in oxygen consumption. In Fig. (37) are reported four cases with CBF decline, but only one patient evolved to brain death due to global hypoperfusion.

Low global CBF levels are more frequently found in the early hours post injury [38,59]. Some of these cases are associated to true ischemia as shown by the strong association with early mortality [38,59] and low CPP values [58]. Global low CBF values can be found in patients with not evacuated SDH [102]. This finding is probably common in comatose patient with not evacuated mass lesion, but they are rarely described in the literature because measurement of CBF before SDH evacuation should not introduce delays in prompt mass evacuation.

High global CBF: this is a not frequent condition. It is more frequent in younger people, in whom it is physiologically justified. Global high CBF values seem to be associated with diffuse brain injury (Fig. 38) and, less frequently, with post-anoxic encephalopathy [103]. According to Kelly [45] high global CBF values are more associated with high ICP and poor outcome.

**Interpretation of Regional CBF**

In TBI stabilized lesions are commonly analysed: post-traumatic cerebral infarction, the contusion/laceration, the subdural hematomas, the intraparenchymal hematoma.

**Posttraumatic Cerebral Infarction (PTCI)**

PTCI has recently been described in a paper by the La-tronico group [103] and includes: 1st territorial cerebral infarction, complete or incomplete; 2nd watershed cerebral infarction; 3rd non-territorial non-watershed cerebral infarction. The most common example of territorial cerebral infarction is the hypodense lesion in the posterior cerebral artery, after an episode of coning. In such cases the rCBF may be low, as expected (Fig. 39) since compression of the afferent artery against the tentorium margin is the cause of macrovascular ischemia. However, high rCBF values instead of low rCBF values can sometimes be found (Fig. 40). We can pose the hypothesis that a short lasting compression of main trunk artery leads to a critical hypoperfusion promoting cytotoxic edema, expressed at CT by a hypodense area, but after the relief of the compression, a reperfusion occurs. Conversely, long lasting compression could be associated with no reflow. Finally, in some cases, the hypotension may be associated with normally depressed rCBF (Fig. 41). Similar find-
ings have been described by the Robertson group [104]. Watershed cerebral infarction can sometimes be found in patients with low CPP during the core phase in ICU management (Fig. 42). Non territorial non watershed infarction with multiple scattered hypoattenuation areas are sometimes found in patients who developed prolonged low CPP states [105]. These are more frequently due to primarily high ICP occurring in the early acute phase, sometimes before the evacuation of acute SDH [106], and presenting with severe clinical findings, GCS 3, bilateral midriasis, or in patients with initial secondary damage, hypoxia, hypotension, anemia. In patients affected by chronic arterial hypertension and intracranial hypertension, such areas may be the result of inappropriate CPP values in relation to a chronic rightward shift of autoregulation curve (Fig. 43).

**Traumatic Contusion/Laceration and Traumatic Hematoma**

CBF in traumatic contusion and traumatic hematoma seems to be distributed in a concentric gradient consistent with an increase in CBF from the center to the periphery of the lesion. Schematically, the lesion may be subdivided into three ROIs: the hemorrhagic core, the perilesional low density area and the normal appearing area surrounding the edema. This method has been extensively described (Fig. 44) [75] and successfully applied with perfusion computerized tomography [107]. Among the various imaging modalities,
Fig. (39). Post traumatic cerebral infarction (PTCI) associated with deep ischemia. This is a territorial PTCI involving the posterior cerebral artery (PCA) supply territory.

Fig. (40). Post traumatic cerebral infarction (PTCI) associated with focal hyperemia. This is a territorial PTCI involving the posterior cerebral artery (PCA) supply territory.

Fig. (41). Post traumatic cerebral infarction (PTCI) associated with mildly reduced CBF. This is a territorial PTCI involving the posterior cerebral artery (PCA) supply territory.
Xe-CT in Head Injury

Xe-CT is the most employed technique for assessment of intraparenchymal lesions. Low rCBF values in the core and in the perilesional low density area are commonly found [36,53,104,108-110]. Intraparenchymal lesions are not a homogenous category and at least two macro subtypes can be distinguished [111]: traumatic contusions, in which the central edematous area surrounds or includes several bleeding focii, and traumatic hematomas, in which a well defined and prominent hemorrhagic core is circularly surrounded by edema. In 109 intraparenchymal lesions, we showed that low CBF values are more commonly found in the edematous area surrounding the hemorrhagic isles in traumatic contusion (29.7 ± 19.6 ml/100 gr/min) than within the intralesional edematous area in traumatic hematoma (35.1 ± 21.3 ml/100gr/min) [112] Fig (45). These physiological findings suggest that the two lesions could be characterized by a different pathophysiology [113, 114]. Presumably, the edematous-hemorrhagic core of the lesion is deeply affected by the primary destructive damage which includes a focal cerebral ischemia. Conversely, in traumatic intracranial hematomas, peri-lesional edema probably evolves towards an inflammatory reaction, with less CBF disturbance.

Fig. (42). Watershed post traumatic cerebral infarction (PTCI) involving the areas between posterior cerebral artery (PCA) and middle cerebral artery (MCA) and border zones within the white matter (arrows). Multiple infarctions were probably due to several drops in cerebral perfusion pressure (CPP), due to refractory increases in intracranial pressure (ICP).
Decreased perfusion in intraparenchymal lesions represent a multifactorial phenomenon promoted by an increase in segmental arteriolar [115] and capillary resistance due to the swelling of the astrocytes endfoot [108], impairment of capillary network [116], and of oxygen diffusion [117]. Although correction of CBF impairment within and around the lesion seems to be indicated, the optimal therapeutic option remains to be defined. In this regard, Xe-CT may be able to verify the effect of physiological changes on intralesional rCBF. Hypocapnia, through hyperventilation, has been extensively applied to reduce intracranial hypertension. In fact, the vasoconstriction of pial arterioles and precapillary arteri-

Fig. (43). A patient affected by chronic hypertension with bifrontal traumatic contusion developed intracranial hypertension. Mean daily values of cerebral perfusion pressure (CPP) were apparently adequate. However, the time course of the minimum daily CPP and the maximum intracranial pressure (ICP) values revealed values which were probably critical for patient physiology. The patient developed multiple scattered PTCI.
Fig. (44). Traumatic contusion and the ROI analysis according to Chieregato et al. [75]. Three different regions of interest (ROIs) larger than 1 cm² were drawn freehand on the diagnostic CT: 1) within the traumatic hematoma proper (hemorrhagic core); 2) surrounding the hematoma low-density area (perihematoma low-density area); 3) within 1 cm of the normal-appearing brain tissue surrounding the perihematoma low-density area (perihematoma normal-appearing area).

Fig. (45). Regional CBF values (on the y axis, CBF expressed in ml/100gr/min) from intraparenchymal lesion measured in hemorrhagic core (core), in perihematoma low-density area (intra low), in perihematoma normal-appearing area (peri normal).

It may be observed that median values of rCBF in intrallesional edema (intra low) are lower in traumatic contusion toward intraparenchymal traumatic hematoma. Data from 125 Xe-CT studies.

The dashed line indicate the traditional CBF threshold of ischemia of 18ml/100gr/min [49].

Hypocapnia reduces the cerebral blood volume and, as a function of the cerebral compliance, reduces ICP as well [118]. However, hypocapnia can also result in CBF reduction. Marion [53] and McLaughlin [52], by means of double test change of PaCO₂, showed that, beside global reduction in CBF, hypocapnia is also responsible for rCBF decrease in the pericontusional edematous area. While doubts have been reported on the real consistence of ischemia related to hypocapnia in apparently normal tissue [119], edematous areas seem sensitive to increases in PaCO₂ which may be associated with small improvements in intrallesional rCBF (Fig. 46).

A further therapy, commonly used by neurointensivists, is the induction of an increase in CPP to control ICP [120,121], and to improve local rCBF [122]. Regarding focal hypoperfusion, however, clinical studies by means of PET have shown only minor improvements in rCBF in intrallesional edematous area following CPP elevation [123]. In a subsequent study [57], we showed that only intrallesional lesions with low critical rCBF within the intrallesional edematous area can gain a minor improvement (Fig. 47). This increase, however, was too shallow to be of clinical relevance. Conversely, patients with relatively high rCBF showed a consistent reduction in rCBF in response to CPP elevation. It may, therefore, be hypothesized that microcirculation becomes structurally affected by ischemia with associated impaired autoregulation in patients with low rCBF. However, due the paucity of recruitable microvessels, only a minor improvement can be obtained. Conversely, when a preserved baseline rCBF is found in areas with vasogenic edema [124] and a damaged blood brain barrier (BBB), a sudden increase in CPP could be responsible for a further BBB breakdown [125] and noradrenaline diffusion outside
In this situation, noradrenaline could result in a vasoconstrictory effect on sensitive and autoregulating arterioles [128]. This paradoxical reduction in rCBF was observed even in aneurysmal subarachnoid by Darby [129].

**Acute Subdural Hematoma**

Cerebral blood flow measurements in regions underlying acute SDH have rarely been obtained [102]. Before surgical evacuation, low CBF values can probably be found due to a local compressive effect with distortion and deeply reduced CPP [106]. After evacuation, complex mechanisms are involved and the cortex underlying the evacuated SDH is potentially at risk of further damage. Several CBF patterns can be found in the cortex beneath the evacuated SDH. In many cases, a traumatic contusion is associated and, in such cases, the consequences of SDH on CBF are mixed with those of traumatic contusion. However, in more isolated SDH, all

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**Fig. (46).** A patient with a satellite contusion below an evacuated subdural hematoma (SDH). An induced increase in end tidal CO₂ (EtCO₂) was induced (from 28 to 34 mmHg) and was associated with an improvement in rCBF in the traumatic contusion (arrows).

**Fig. (47).** Changes in rCBF in perilesional edematous area after cerebral perfusion pressure (CPP) elevation, induced by means of norepinephrine infusion, during a double Xe-CT test. Patients were separated into those in whom a small improvement was obtained and into those in whom a paradoxically rCBF reduction was detected. These contusions have a low baseline value. In other contusions a reduction in rCBF was observed in association with higher baseline rCBF values. The changes in rCBF were less pronounced and less associated to baseline values in perilesional normal appearing area.
CBF ranges can be found beneath the evacuated SDH: a focal CBF depression, frequently due to associated intraparenchymal lesion (Fig. 48), but sometimes in apparently normal tissue (Fig. 49), or normal posttraumatic CBF reduction (Fig. 50), or a minor reduction in rCBF, at least in comparison with contralateral side (Fig. 51), or a dense focal hyperemia with elevated values compared to contralateral hemisphere (Fig. 52). This finding had already been observed by Marion [72] and Astrup [56], while our group found that hyperemia was frequent and prolonged only in patients with unfavourable outcome [44].

The Future of Xe-CT in TBI Patients

We believe that, in the next few years, TBI patients would be better characterized by means of integration between imaging and focal monitoring. While PET will probably remain dedicated to research, in clinical settings Magnetic Resonance Imaging could provide a quantitative mapping of water distribution, the type of edema (cytotoxic or vasogenic) and the mapping of metabolites (Magnetic Resonance Spectroscopy), Xe-CT an accurate CBF mapping of CBF, and CT perfusion information regarding CBF (semiquantitative), CBV and BBB permeability. These data, obtained as a snapshot, can be integrated with focal monitoring, PtiO2, TD-rCBF or microdialysis, especially if placed in the injured tissue [6-8]. Unfortunately, interpretation of regional monitoring is sometimes hypothetical because not coupled to rCBF measurement [130]. We can suppose that, in the future, as a consequence, an interplay between imaging and focal monitoring will become a daily occurrence: focal disturbance can be detected by imaging and guide the placement of focal monitoring. In return, data from focal monitoring should be validated by imaging that can test the value measured by focal monitoring by means of ROI ana-
lyzing area surrounding the regional sensor tip (Fig. 53). Furthermore, imaging can evaluate whether the regional data is too regional. Once this cross validation is done, monitoring and management strategies could be applied at bedside and further imaging should be planned to verify the efficacy of therapies. These concepts have been debated by Valadka and Robertson in their recent review [131].

While only invasive regional monitoring can currently be used as a proxy or a direct measurement of regional CBF, in the near future, even non-invasive regional measurement of rCBF could be coupled and periodically validated by bedside measurement of quantitative rCBF by means of portable Xe-CT [28]. To date, however, most ICUs are located at a distance from neuroimaging: MRI is time consuming and CT perfusion calculations are still too complex and based on indirect assumptions. Fortunately, technology is moving CT to the patient, inside the ICU, instead of moving the patient to the CT [23]. Mobile CT has shown that it reduces time [132] and allows Xe-CT measurement at bedside [3]. The improved availability in neuro-ICU allows the clinician to measure CBF promptly whenever CBF reduction is suspected to be the cause of brain damage. As discussed above, the most important limitation of Xe-CT measurement performed outside the ICU, is represented by the delay between the supposed CBF derangement and its detection, and the consequent delay in targeted therapies. Sturnegk et al. [133] showed that in such a way Xe-CT can be integrated into ICU management.

CONCLUSION

The Authors believe Xe-CT measurement in a neuro-ICU, located in a regional not university hospital, to be a useful tool which can improve our knowledge of CBF physi-
The major limitation of Xe-CT imaging, that is the frequent delay in the prompt detection of rCBF decline before the development of an irreversible cause of ischemia, should be resolved in the near future with the diffusion of portable CT scanners. However, radioexposure remains a persistent limitation of Xe-CT.

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