Overview of Monitoring of Cerebral Blood Flow and Metabolism after Severe Head Injury

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Abstract: The relationships between cerebral blood flow (CBF), cerebral metabolism (cerebral metabolic rate of oxygen, $CMRO_2$) and cerebral oxygen extraction (arteriovenous difference of oxygen, $AVDO_2$) are discussed, using the formula $CMRO_2 = CBF \times AVDO_2$. Metabolic autoregulation, pressure autoregulation and viscosity autoregulation can all be explained by the strong tendency of the brain to keep $AVDO_2$ constant. Monitoring of CBF, $CMRO_2$ or $AVDO_2$ very early after injury is impractical, but the available data indicate that cerebral ischemia plays a considerable role at this stage. It can best be avoided by not "treating" arterial hypertension and not using too much hyperventilation, while generous use of mannitol is probably beneficial. Once in the ICU, treatment can most practically be guided by monitoring of jugular bulb venous oxygen saturation. If saturation drops below 50%, the reason for this must be found (high intracranial pressure, blood pressure not high enough, too vigorous hyperventilation, arterial hypoxia, anemia) and must be treated accordingly.

Résumé: Surveillance du flot sanguin et du métabolisme cérébral après un traumatisme crânien sévère. Nous discutons des relations entre le flot sanguin cérébral (FSC), le métabolisme cérébral (taux métabolique cérébral d'oxygène, $TMCO_2$) et le taux d'extraction de l'oxygène (différence artérioveineuse en oxygène, $DAVO_2$), et nous utilisons la formule $TMCO_2 = FSC \times DAVO_2$. L'autorégulation métabolique peut être entièrement expliquée par la tendance marquée du cerveau à garder la $DAVO_2$ constante. La surveillance du FSC, du $TMCO_2$ ou de la $DAVO_2$ très tôt après le traumatisme est impraticable. Cependant, les données disponibles indiquent que l'ischémie cérébrale joue un rôle considérable pendant cette période. La meilleure façon de l'éviter est de ne pas "traiter" l'hypertension artérielle et de ne pas trop utiliser l'hyperventilation, alors que l'utilisation généreuse du mannitol est probablement bénéfique. A l'unité de soins intensifs, le traitement peut être guidé de façon pratique par la surveillance de la saturation veineuse en oxygène au niveau du golfe de la jugulaire. Si la saturation s'abaisse au dessous de 50%, on doit en trouver la cause (pression intracrânienne élevée, pression sanguine trop basse, hyperventilation trop vigoureuse, hypoxie artérielle, anémie) et on doit y remédier.

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In the past decade a large body of data has become available to deepen our insight into the pathophysiology of severe head injury and impacting its management in the acute stage. Parts of this new knowledge stem from randomized, clinical trails and the conclusions drawn from such trials can be considered to be "absolute"; often parts stem from careful analysis of data generated by new monitoring techniques, especially of cerebral blood flow (CBF) and metabolism, and although the conclusions drawn from those studies are logical, the applications in clinical practice have not been tested in a rigorous fashion and thus should be regarded with caution.

Some Factors in the Relationships between CBF, Cerebral Metabolism and Cerebral Oxygen Extraction

When regarding the following data, a few principles should be kept in mind. The first is that cerebral metabolism is almost entirely dependent on oxidation of glucose, requiring a constant supply of oxygen by cerebral blood flow:

$$CMRO_2 = CBF \times AVDO_2 \quad (1)$$

where $CMRO_2$ is cerebral metabolic rate of oxygen and $AVDO_2$ is arteriovenous difference of oxygen. Under most circumstances $CMRO_2$ is constant, normally 3.2 ml (of O_2)/100g (of brain tissue)/min[1], much lower, but still constant, during coma and much higher during seizures. $AVDO_2$ is approximately 6.5 vol % (ml of O_2/100 ml of blood)[1] and the brain has a very strong tendency to keep this constant, independent of $CMRO_2$ or CBF. Thus, if we consider $AVDO_2$ as a constant in equation (1), CBF will have to follow changes in $CMRO_2$ (metabolic autoregulation or metabolic coupling), while CBF will have to

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remain constant under circumstances of constant $CMRO_2$, despite changes in perfusion pressure (pressure autoregulation)[2] or changes in blood viscosity (viscosity autoregulation)[3] which without compensatory mechanisms would lead to changes in CBF. This leads us to the second principle to be kept in mind, namely the factors that govern CBF:

$$CBF = K\frac{CPP\,x\,d^4}{8\,x\,l\,x\,v} \qquad (2)$$

where k is a constant, CPP is cerebral perfusion pressure in turn defined by mean arterial blood pressure (MABP) minus intracranial pressure (ICP), d is diameter of the blood vessels, l is the length of the blood vessels (which, of course, is practically constant) and v is blood viscosity. By far the most powerful factor in this equation is vessel diameter. For instance, the maximum constriction that can be obtained by hyperventilation is approximately 20% from normal baseline[4], but this leads to a decrease in CBF of almost 60% from a normal value of 50 ml/100g/min to 20 ml/100g/min. It should be noted that practically all of this diameter regulation takes place in the microcirculation, especially in the arterioles with a diameter of 300-15 μ[4,5] The interaction between diameter changes in the larger, conducting arteries and changes in the microcirculation (which are sometimes in opposite directions) and their relationship with $CMRO_2$, $AVDO_2$ and ICP has been discussed by us elsewhere,[6] and are summarized in Figure 7.

Primary Reduction	CBF	CBV (ICP)	$ADVO_2$
$CMRO_2$	⇓	⇓	=
CPP (autoregulation intact)	=	⇑	=
CPP (autoregulation defective)	⇓	⇓	⇑
Blood Viscosity (autoregulation intact)	=	⇓	=
Blood Viscosity (autoregulation defective)	⇑	=	⇓
$PaCO_2$	⇓	⇓	⇑
Conductance vessel diameter (vasospasm above ischemia threshold)	⇓	⇑	⇑

Figure 1: *Changes in cerebral blood flow (CBF), cerebral blood volume (CBV), and intracranial pressure (ICP), and arteriovenous difference of oxygen ($AVDO_2$) with primary reduction of various features (cerebral metabolic rate of oxygen, $CMRO_2$ and cerebral perfusion pressure, CPP) and with vasospasm.*

The third important factor to be kept in mind is that whereas in both metabolic and pressure autoregulation vessel diameter changes are compensatory responses to maintain $AVDO_2$ constant, in CO_2 responsitivity the diameter changes are primary and CBF and $AVDO_2$ will follow passively. Thus, CO_2 reactivity differs from any type of autoregulation in that $AVDO_2$ changes and that it is not some sort of adaptation response of the brain to changing circumstances. Whereas the "purpose" of autoregulation can be quite obvious, e.g. protect the brain against the occurrence of ischemia during shock, the "purpose" of CO_2 reactivity is unclear.

Early Postinjury Ischemia

It had been suspected for a long time that cerebral ischemia, defined as CBF not being able to meet the metabolic demands of the brain tissue, plays an important role after severe head injury. This suspicion was based, for the most part, on autopsy findings of histological damage indicative of cerebral ischemia in 80% of patients who died, even though most of those patients had adequate CPP during the period in which this was monitored.[7] On the other hand, however, in a large number of studies in which CBF was measured, flow values below the threshold of ischemia (usually taken as 18 ml/100g/min)[8] were hardly ever found.[9-17]

Moreover, in the first study to report on a sizeable number of $AVDO_2$ measurements, critically high values of $AVDO_2$ indicative of ischemia were also extremely rare.[17] We speculated, however, that most of these measurements were not obtained early enough after injury and the first, preliminary data supporting this view were published in 1984.[18] Later, we presented results of measurements of CBF in 186 adult patients, using the ^{133}Xe technique in the intensive care unit (ICU).[19] These data are summarized in Table 1. Although the average $AVDO_2$ in the first few hours was 7.1 vol %, it should be noted that in those patients in poor clinical condition (Glasgow Coma Score, GCS, 3 and 4),[20] it was 8 vol %, which after severe injuries comes close to indicating cerebral ischemia.[19] Obviously, the incidence of ischemia very rapidly diminishes over time and as the earliest measurements with ^{133}Xe were done at 4 hours post injury, the question as to what the situation would be even earlier after injury remained unanswered from that study. Moreover, no patients with intracranial mass lesions were included, in which the highest incidence of ischemia could be expected.

Using the stable Xenon-CT technique, CBF can now be calculated during the initial, diagnostic CT scan. Patients with mass lesions still *in situ* can also be studied with this technique, but the additional 10-30 minutes of time necessary for the CBF study leads to an under-representation of those with very large lesions causing major brain shift or those with ominous clinical

Table 1. Cerebral Blood Flow and Arteriovenous Blood Oxygen Differences in Head-Injured Patients Measured at 6-Hour Intervals Postinjury*

Hours Post-injury	CBF (ml/100gm/min)	$AVDO_2$ (ml/100 ml)	No. of Cases Studied	No. (%) with Ischemia
4-6	22.5 ± 5.2†	7.1 ± 1.5™	12	4 (33%)
6-12	29.0 ± 10.0	6.3 ± 2.5™	74	8 (11%)
12-18	33.3 ± 11.0	4.7 ± 1.6	50	0 (0%)
18-24	34.8 ± 11.4	4.7 ± 1.6	37	2 (5%)
24-30	33.9 ± 10.4	4.4 ± 2.4	29	1 (3%)
30-36	33.2 ± 12.0	4.6 ± 1.4	23	1 (4%)
36-42	36.9 ± 12.7	4.2 ± 1.7	19	1 (5%)
42-48	34.8 ± 14.7	3.9 ± 1.1	11	0 (0%)
>48	33.6 ± 12.2	4.4 ± 1.6	129	7 (5%)

*CBF = Cerebral blood flow; $AVDO_2$ = arteriovenous difference of oxygen content. Ischemia is defined as CBF ≤ 18 ml/100gm/min.
†Significantly lower than values at all later time intervals (Newman-Keuls' test, $p < 0.05$).
™$AVDO_2$ values in the first 12 hours postinjury were significantly higher than values of later intervals (Newman-Keuls' test, $p < 0.05$).
Adapted from Bouma et al.[19] with permission.

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signs such as pupillary abnormalities, because these patients are taken to the operating room without the slightest delay. Results from stable Xenon-CT scanning in 32 patients were presented and extensively discussed earlier,[21] but this initial series has now been expanded to 92 patients, whose data are shown in Tables 2, 3, and 4. It should be noted that all 92 patients, including the 32 discussed earlier,[21] are represented in these tables, except for the six months outcome data in Table 4, which were not available as yet for all subjects. It can be assumed, however, that the number of comatose and awake patients will increase but the proportion between the two will remain about the same, while the proportion of dead patients will drop as most deaths occur within 2-3 months from injury. The following conclusions can be drawn:

1) Cerebral ischemia is a very early event after severe head injury and disappears, either spontaneously or after operative evacuation of mass lesions.[22] 2) Acute subdural hematoma and diffuse cerebral swelling (absence of basal cisterns) are the CT diagnoses most often associated with cerebral ischemia. The low incidence of ischemia with epidural hematoma is certainly caused by the fact that in patients with urgent indication for operation CBF was not measured. 3) The prognosis of patients with ischemia is extremely poor.

Although it has been argued that our definition of ischemia (CBF < 18ml/100g/min) would not necessarily indicate insufficient cerebral perfusion, but might be a normal adjustment of CBF to extremely low $CMRO_2$ (coupling of CBF and $CMRO_2$)[23], we feel that our early high $AVDO_2$ values argue against such a position[24] and measures should be taken to at least not aggravate ischemia and rather to possibly prevent or treat it altogether.

Table 2. Time Course of Regional Ischemia*

Time of Study	Total	Regional Ischemia	No Ischemia
0.7-4 Hours	58	16 (28%)	42 (72%)
4-8 Hours	15	3 (20%)	12 (80%)
8-24 Hours	29	0 (0%)	29 (100%)

*Regional ischemia = cerebral blood flow of ≤ 18 ml/100g/min in one entire lobe or basal ganglia or brain stem.

Table 3. Initial CT Findings and Incidence of Regional Ischemia*

CT Findings	No. of Cases	Ischemia
Epidural Hematoma	5	0%
Subdural Hematoma	22	41%
Focal Contusions	36	6%
Diffuse Swelling	16	50%
Normal	13	0%

*Regional ischemia = cerebral blood flow of ≤ 18 ml/100g/min in one entire lobe or basal ganglia or brainstem.

Table 4. Outcome Modalities of Patients with and without Regional Ischemia*

Outcome	Regional Ischemia		No Ischemia	
	48 Hours	6 Months	48 Hours	6 Months
Dead	14	14	4	17
Comatose	5	2	57	5
Awake	0	3	11	45

*Regional ischemia = cerebral blood flow of less or equal than 18 ml/100g/min in one entire lobe or basal ganglia or brainstem.

Management of Early Ischemia

It is not practical under most circumstances to measure CBF during the first, diagnostic CT scan and this should be considered research, albeit with very practical applications. Moreover, the other method to detect cerebral ischemia, i.e. determination of $AVDO_2$ or $SjvO_2$ (saturation of jugular venous oxygen, see below), is also not easily accomplished during the first few hours post-injury, exactly at the time that ischemia does occur. Thus, we should simply assume that cerebral ischemia is present, until proven otherwise. The principles to treat this by improving CBF can easily be grasped by considering equation (2), and some of these treatments are clearly in contrast with earlier teachings, when most emphasis was placed on diminishing ICP and prevention of brain edema. The first factor in equation (2) which can be manipulated to raise CBF is CPP, determined by MABP and ICP. Of course, rapid evacuation of intracranial mass lesions to decrease ICP and thus improve CPP is still the cornerstone of our early efforts to improve CBF and prognosis, and is proven to be effective.[22,25,26] Another means of decreasing ICP is by diminishing cerebral blood volume (CBV), which can be accomplished with hyperventilation. CO_2 reactivity is usually intact after severe head injuries, albeit diminished in the first few hours.[27] However, despite the increase in CPP, CBF practically always goes down with hyperventilation[17,27], due to the fact that vessel diameter in equation (2) is to the fourth power. Moreover, we have shown that *preventive* hyperventilation retards clinical improvement after severe head injury[28], although we do not want to imply here that that occurs because of induction or aggravation of early ischemia. Finally, Obrist has published data showing that a severely head injured patient with low CBF and low $AVDO_2$ (and thus low $CMRO_2$) (further) hyperventilation leads to further decrease in CBF with concomitant rise in $AVDO_2$.[29] However, in a number of patients, the relative rise in $AVDO_2$ was larger than the relative decrease in CBF, resulting in a paradoxical and unexplained increase in $CMRO_2$. Whether this increased $CMRO_2$ with hyperventilation is an improvement is debatable and, in fact, we feel it is detrimental. Suppression of $CMRO_2$ early after injury by inducing mild hypothermia leads to improved outcome, as has been shown by Marion and coworkers.[30] Taken altogether, unless there is a unilateral pupillary abnormality, we advocate normocapnia early after severe head injury, although impaired pulmonary function often forces us to use mild hyperventilation ($PaCO_2 \simeq 35$ mmHg) in order to maintain optimal arterial oxygenation.

Another way of increasing CPP would be by raising MABP. In the past, and also recently, it has been advocated to treat the arterial hypertension that often accompanies severe head injuries, mostly in the hope of diminishing cerebral edema caused by blood brain barrier breakdown.[31-33] However, there are no data to indicate that the blood brain barrier is indeed defective after severe head injury and we actually have data indicating the contrary, except in cases of contusions (unpublished data, Marmarou A and Muizelaar JP). Moreover, treating

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arterial hypertension under these circumstances has not been put to the test in any clinical trial, and it is almost certain to aggravate (border line) cerebral ischemia if present, which is 30-50% of the time. Therefore, we consider arterial hypertension early postinjury as a physiological response to cerebral ischemia (Cushing response) until proven otherwise, and it should best be left alone. It should be emphasized here, however, that such a management policy is solely based on interpretation of early CBF, $AVDO_2$ and $CMRO_2$ data and has also not been put to the test in any rigorous fashion.

A completely different matter is, of course, the treatment of hypotension. If autoregulation is defective, CBF is directly and linearly related to blood pressure, while if autoregulation is intact arterial hypotension can lead to considerable increase in ICP.[34-35] Thus, depending on the status of autoregulation maintaining a normal blood pressure or inducing some arterial hypertension can either lead to improved CBF or diminished ICP or both.[18,19,34-37] A final way to influence CBF is by manipulating blood viscosity, which is also linearly related to CBF. Thus, with ischemia and viscosity autoregulation is absent[3], we can double the prevailing CBF by slashing blood viscosity in half. The latter occurs when hematocrit (Hct) is reduced from 45-50% to 30-33%, although this reduction also leads to a decrease in arterial oxygen content by 30%. However, doubling the flow of blood with only 70% of the oxygen, still leads to an increase of 40% in total oxygen delivery and therefore we always aim to maintain Hct between 30 and 35%. Reductions of Hct below 30% do not result in much further viscosity change while oxygen content falls precipitously. Through its effect on Hct and also on erythrocyte volume and deformability, mannitol has a considerable beneficial influence on blood viscosity.[38] Combined with its cerebral dehydrating effect, mannitol therefore either diminishes ICP or increases CBF or both, the balance between the two effects partly dependent on the status of autoregulation. When we consider that mannitol is also a scavenger of the hydroxyl anion oxygen radical species and consider the role of oxygen radicals after severe head injury[41], it can easily be seen that we use mannitol generously, especially early after injury when raised blood osmolality is of no concern as yet.

Subacute Postinjury Cerebral Ischemia or Hypoxia: Monitoring

With most established techniques for CBF measurements, such as nitrous oxide clearance, ^{133}Xe clearance or stable Xe-CT scanning, it is impossible to monitor CBF continuously and impractical to even do this frequently. Thermodilution CBF monitoring is a technique yielding continuous data,[42,43] but it demands that an epicortical probe is left behind at surgery or implanted in a separate procedure, while it also only gives very local CBF values and its usefulness after severe head injury has not been established yet.[44] Blood velocity measurement with transcranial Doppler (TCD) ultrasound is a noninvasive, easily applied technique that can give some indication of CBF, especially when the Lindegaard index[45] is used, and Martin et al. have shown that TCD is useful for the detection of ischemia, caused by cerebral arterial vasospasm.[46] However, this cause for ischemia appears to be very rare and even if it occasionally occurs, it will announce itself when $SjvO_2$ is continuously monitored (see below).

The search for a continuous monitor for the adequacy of cerebral oxygenation has led to the introduction of measuring the saturation with oxygen of venous blood in the jugular bulb.[47-49] When one considers equation (1) and assumes that $CMRO_2$ remains unchanged with sufficient oxygen supply, $AVDO_2$ can be used as an estimate of CBF.[50] Venous oxygen content, in turn, can be estimated from oxygen saturation, which can be measured continuously with a fiberoptic catheter similar to that used for umbilical vein monitoring in the newborn (Oxymetrics®, Abbott Labs), but now introduced in the jugular vein and retrogradely placed in the jugular bulb. A good correlation between *changes* in $SjvO_2$ and CBF has also been described.[51] When saturation is low (generally considered low when $SjvO_2 < 50$-55%), this means that $AVDO_2$ is abnormally high, indicative of ischemia, unless arterial saturation is also very low or (arterial) hemoglobin level is very low. Whatever the case may be, $SjvO_2$ monitoring can tell whether oxygen supply to the brain is matched with metabolism, and if it is low the cause for this mismatch must be found (after checking and calibration of the catheter) and corrected.

Others have defined jugular bulb desaturation as $SjvO_2 < 50\%$ for five minutes or longer and we have adopted these guidelines as well. When this occurs, one should first check the light intensity of the fiberoptic device. In a very large number of cases, light intensity is too low because the catheter is lodged against the wall of the blood vessel and by simply rotating the patient's head slightly or wiggling the catheter a little, this can be corrected. If the light intensity is sufficient or the above-mentioned measures are insufficient, one should draw a blood sample through the catheter, together with an arterial sample, to calibrate the device. In general, the correlation between the apparatus' reading and the actual blood gases is very good, but for an indepth discussion of the validity and representativeness of the jugular bulb oxygen tension, the reader is referred to the article by Stocchetti et al.[52] An important point, not discussed in that article, is that the number of "false alarms" with this monitoring technique is high (> 50%, Robertson, personal communication) but the number of missed periods of ischemia appears to be extremely low or nonexistent. Thus, no false sense of security is induced, but at the cost of frequent, "unnecessary" checks.

Recently, the Baylor College of Medicine group has provided an update on their experience with $SjvO_2$ monitoring.[51] As noted above, desaturations were defined as $SjvO_2 < 50\%$ for at least five minutes and confirmed with a jugular blood sample measurement. Most of these desaturations took place during the first 48 hours of monitoring and did not last much longer than 15 minutes, as corrective measures were successful. An exception was the desaturation due to high ICP, which generally occurred later (up to 7 days) and would last much longer as high ICP was sometimes intractable.

Table 5, adapted from Gopinath et al.[51] indicates the reasons for jugular bulb desaturations, and in Table 6, generated by the same group, the strong correlation between the number of desaturations per patient and poor outcome is clearly depicted.

Subacute Postinjury Cerebral Ischemia or Hypoxic Management

Depending on the cause for the desaturation, appropriate therapeutic action can be taken. When too vigorous hyperventilation is present, the CO_2 can be allowed to rise or, if the hypocapnia is still necessary for ICP control, it can be combined with mannitol so as to both decrease ICP and stimulate CBF.[53]

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Table 5. Jugular Desaturation < 50% in 116 Patients.

Systemic Causes	
Hypocarbia	21
Hypotension	8
Arterial Hypoxia	
Anemia	
Cerebral Causes	
Intracranial Hypertension	34
Cerebral Vasospasm	1
Combination of Systemic and Cerebral Causes	6
Total Number	77

*Adapted from Gopinath et al.[51] with permission.

Table 6. Jugular Desaturation < 50% in 116 Patients*

No. of Desaturation	Good Recovery/ Moderate Disability	Severe Disability Vegetative	Dead
0	45%	39%	16%
1	26%	32%	42%
Multiple	10%	20%	70%

*Relationship between confirmed episodes of jugular desaturation and outcome at 3 months in 116 patients.
*Adapted from Gopinath et al.[51] with permission.

Gopinath et al.[51] also described how the use of a diuretic (furosemide) leads to hypotension secondary to hypovolemia with low central venous pressure (CVP) with resulting desaturation. This could be corrected by rapid administration of fluids such as albumin solution, rather than by using an alpha-adrenergic drug to raise the blood pressure. For some other causes of desaturation, the treatment is quite obvious: give blood for anemia, adjust ventilator settings for arterial hypoxia, raise the blood pressure for vasospasm (similar as is done for treatment of vasospasm with subarachnoid hemorrhage[36]). Maintaining CPP above 70 mmHg, even if ICP cannot be kept below 20 mmHg, by raising the MABP ("CPP management") as proposed by Rosner and Daughton,[54] probably is also beneficial through its prevention of jugular bulb desaturations. Again, in practice, this is accomplished in the same way as vasospasm after SAH is treated: maintain good volume status with ample fluids including albumin solution so as to keep CVP at 10-15 cm H_2O, and use an alpha-adrenergic drug to induce hypertension. There are data supporting the use of albumin 25-50 ml/hr over other colloid solutions[55], while we prefer phenylephrine (neosynephrine) 80 mg/250 or 500 ml normal saline) for reasons explained elsewhere.[36] However, CPP management has not been subjected to a randomized trial to prove its beneficial effect. Nevertheless, along with other changes in treatment based on measurements of CBF, $AVDO_2$, $CMRO_2$ and $SjvO_2$ providing a better insight into the pathophysiology of severe head injury, CPP management has taken its place in our armamentarium to improve outcome.

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