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Early Ischaemia After Severe Head Injury
Preliminary Results in Patients with Diffuse Brain Injuries

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Summary

Ischaemic brain lesions still have a high prevalence in fatally head injured patients and are the single most important cause of secondary brain damage. The present study was undertaken to explore the acute phase of severely head injured patients in order to detect early ischaemia using Robertson's approach of estimating cerebral blood flow (CBF) from calculated arterio-jugular differences of oxygen ($AVDO_2$), lactates (AVDL), and the lactate-oxygen index (LOI).

Twenty-eight cases with severe head injury were included (Glasgow Coma Scale Score below or equal to 8). All patients but one had a non-missile head injury. All the patients had a diffuse brain injury according to the admission CT scan. ICP measured at the time of admission was below 20 mmHg in 17 cases (61%). All patients were evaluated with the ischaemia score (IS) devised in our center to evaluate risk factors for developing ischaemia. Mean time from injury to the first $AVDO_2$/AVDL study was 23.9 ± 9.9 hours.

According to Robertson's criteria, 13 patients (46%) had a calculated LOI ($-$ AVDL/$AVDO_2$) value above or equal to 0.08 and therefore an ischaemia/infarction pattern in the first 24 hours after the accident. Of the 15 patients without the ischaemia/infarction pattern, in three cases the CBF was below the metabolic demands and therefore in a situation of compensated hypoperfusion. No patient in our series had hyperaemia. Comparing different variables in ischaemic and non-ischaemic patients, only arterial haemoglobin and ischaemia score (IS) was significantly different in both groups. The ischaemia score had mean of 4.3 ± 1.7 in the ischaemic group and 2.7 ± 1.4 in non-ischaemic patients ($p = 0.01$). It is concluded that ischaemia is highly prevalent in the early period after severe head injury. Factors potentially responsible of early ischaemia are discussed.

Keywords: Head injury; ischaemia; lactates; cerebral metabolism; arteriovenous oxygen differences; cerebral blood flow; arterio-jugular differences.

Introduction

Cerebral ischaemia refers to the inadequate delivery of oxygen to the brain, whether due to decreased arterial oxygen content, decreased cerebral blood flow (CBF), increased metabolic requirements or impaired tissue uptake[59]. Ischaemic brain lesions have a high prevalence in fatal non-missile head injured patients and are the single most important cause of secondary brain damage[46]. It has been well established that in severe head injury, global or local CBF derangements are common[16, 45, 46, 50, 53, 54, 56, 59, 63, 67, 72], ischaemia or hyperaemia being frequently found in the acute phase. CBF is under normal conditions tightly coupled to the oxygen metabolism. This adjustment is made by very elaborate mechanisms. These mechanisms are deranged in many cases of severe head injury producing an uncoupling of the CBF from the cerebral metabolic rate of oxygen ($CMRO_2$). Trying to identify when uncoupling of CBF and $CMRO_2$ is present is very important in clinical practice for two main reasons: to avoid and detect early ischaemia and to rationally select and control therapeutic measures directed to treat intracranial hypertension. Prevention and early treatment of ischaemic disorders is one of the primary aims in modern treatment of severely head injured patients. Theoretically, it could become possible that early recognition and management of ischaemia might prevent in some cases the development of irrecoverable brain tissue necrosis.

Measuring global or regional CBF has been the dominant way of detecting ischaemia in head injured patients[12, 15, 16, 21, 40, 45, 48, 52, 55, 56, 59, 63]. Apart from some methodological problems, most procedures of measuring CBF are technically complex and not available at the bedside. Using positron emission tomography (PET) Baron demonstrated, that local CBF could be

normal, low or hyperaemic regardless of having a complete ischaemic stroke[9].

Arterio-jugular differences of oxygen ($AVDO_2$) have been introduced in clinical practice as an estimate of CBF to $CMRO_2$ coupling[9, 17–20, 55, 60, 62, 63]. According to some authors, hyperaemic or ischaemic patterns can be predicted from $AVDO_2$[9, 18–20, 55, 63]. Nevertheless, some studies have shown that $AVDO_2$ can be misleading in the presence of ischaemia[60, 62, 63]. As a result of this factor, in clinical practice it is very important to have markers that allow clinicians to know the presence of an evolving clinical infarction that makes $AVDO_2$ inaccurate and not useful in estimating CBF. Recent studies from Robertson *et al.*[60, 62, 63] have validated this fact and suggested an alternative approach of using $AVDO_2$ to estimate CBF in brain injury. In Robertson's study, $AVDO_2$ and arterio-jugular differences of lactates (AVDL) were studied together with global CBF and the lactate-oxygen index (LOI) defined as $-AVDL/AVDO_2$. This method allows differentiation between patients with an ischaemic pattern in whom $AVDO_2$ are not estimates of CBF from those without ischaemia in whom $AVDO_2$ does predict CBF[60, 62, 63].

The present study was undertaken to explore the acute phase of severely head injured patients in order to detect early ischaemia using Robertson's approach of estimating CBF from calculated arterio-jugular differences of oxygen and lactates.

Clinical Material and Methods

All the patients admitted with a closed or penetrating head injury and a Glasgow coma score below or equal to 8 from July 1, 1990 to June 31, 1991 were considered for inclusion in the protocol of study only if they fulfilled the following criteria: 1) Time interval from accident to the first computed tomography (CT) scan less or equal to 12 hours and 2) that they have a diffuse brain injury on the admission CT scan. Diffuse brain injury was diagnosed in all patients with no deviations of the midline and no focal lesions above 25 ml.

As a rule, on admission to our emergency room, patients with a head injury are evaluated by members of the anaesthesiological, orthopaedic, intensive care unit (ICU) and neurosurgical staff and multidisciplinary resuscitative measures are taken. According to the first CT scan, we classified all the cases with a diffuse brain injury (DBI) in one of the three categories described before[64, 65] and that in summary are the following:

Diffuse brain injury (DBI) I: In this pattern, we considered all patients in whom the CT scan did not show any abnormality except for more or less severe subarachnoid haemorrhage.

DBI II: Patients in whom the CT scan demonstrated a diffuse brain swelling of varying severity with or without subarachnoid haemorrhage. Radiological findings in this group included partially or completely obliterated basal cisterns, third ventricle and/or symmetrical reduction of lateral ventricles.

DBI III: In this pattern, we included all patients in whom the CT scan showed patterns of DBI I or DBI II and in addition single or multiple intracerebral haemorrhages less than 2 cm in diameter and/or intraventricular haemorrhages.

The intracranial epidural pressure was continuously monitored in all patients. Every severely head injured patient admitted to our institution receives the same initial treatment protocol which includes immediate neurological evaluation and endotracheal intubation with controlled ventilation. Mass lesions with midline shift are operated on, immediately. All patients are admitted to the intensive care unit. Patients with elevations of the intracranial pressure (ICP) are treated with mannitol and hyperventilation if ICP rises above 20 mmHg. In refractory increases of ICP we use barbiturates. Dexamethasone is not usually given in our hospital. Routine medication includes phenytoin, fentanyl, furosemide, pancuronium, and mannitol.

In all the cases, mean arterial blood pressure (MABP), mean ICP and cerebral perfusion pressure (CPP) are routinely monitored. Clinical data for all severe head injury patients in this study was available from the prehospital reports, records from referral centers, the emergency room form and the intensive care unit data sheets. Time interval from accident to admission in our hospital (TIA) and the presence of early extracranial systemic insults (anaemia, hypotension, and hypoxia) were recorded in all patients. The following data were calculated during the 12 hours before the first $AVDO_2$ was measured: mean ICP, mean SABP, mean CPP, lower CPP, and SABP. To evaluate risk factors that predisposed to brain ischaemia in each patient, we devised an Ischaemia Score (IS) to have a measurable scale to grade patients at risk of having ischaemic insults.

Table 1. *Ischaemia Score*

	Score		Score
Subarachnoid haemorrhage*		SaO_2 (%)	
No	0	> 90	0
Yes	1	⩽ 90	1
Hypotension (mean BP)		temperature (°C)	
> 90	0	⩽ 38	0
70–90	1	> 38	1
50–70	2		
< 50	3		
Mean ICP		TIA (hours)+	
< 20	0	⩽ 3	0
20–40	1	< 3	1
> 40	2		
Mean CPP		haemoglobin (grs/dl)	
> 60	0	⩾ 12	0
⩽ 60	1	8–11	1
		< 8	2
Hypoxia (pO_2)		total IS score	0–13
> 60	0		
⩽ 60	1		

* Evaluated in the admission CT scan. + Time from impact to admission in our center.

On this scale, 10 items were evaluated in each patient at the moment of the arterial and jugular blood extractions. Each risk factor was assigned an arbitrary value of 1 to 3. The minimum possible score is 0 points and the maximum 13 points (Table 1).

Immediately after admission, a radial artery was canalized in every patient and a 14 G catheter inserted percutaneously into the internal jugular bulb using the technique described by Goetting *et al.*[27–29]. The catheter was placed on the right side in all but 2 cases. X-ray verification of the catheter position was obtained in all patients prior to obtaining blood samples. Two cases were excluded because of inadequate positioning of the jugular catheter. Arterial and jugular blood samples were obtained at the same time, at least once every 24 hours for the first 3 days after injury. Blood gases, haemoglobin, oxygen saturation and lactate concentration were measured. Blood gases were analyzed on a BGM Instrumentation Laboratory, model 1312+.

Lactate samples were obtained, placed on ice and transported immediately to the laboratory. Samples were then centrifuged and the decanted fluid was kept at − 20 °C until the estimations were undertaken. Whole blood lactate concentration was measured by an enzymatic method using the HITACCHI 717 System*. The coefficient of variation of repeated samples was 2.3%.

Arterio-jugular differences of oxygen ($AVDO_2$) and lactates (AVDL) were calculated once daily for 3 consecutive days after injury. $AVDO_2$ were calculated using the following equation: $AVDO_2 = 1.34 \times Hb[SaO_2 - SvO_2]$, where Hb is arterial haemoglobin and SaO_2 and SvO_2 are the percentage of saturated oxyhaemoglobin in the arterial and jugular blood, respectively. $AVDO_2$ were expressed in µmol/ml uncorrected for pCO_2. AVDL were calculated substracting the venous content from the arterial content of lactate, these differences were also expressed in µmol/ml. Arterial lactates below 1.25 µmol/ml were considered as normal. As an index of anaerobic metabolism, we obtained in all cases the lactate oxygen index (LOI) proposed by Robertson *et al.*[60, 62, 63], LOI was calculated as $-AVDL/AVDO_2$.

This study is based on the results acquired within the first 24 hours after the accident. According to the classification proposed by Robertson *et al.*[63], all the patients with a LOI $\geqslant 0.08$ were considered as having an ischaemia/infarction pattern while in those cases with a LOI < 0.08, ischaemia was considered not to be present. In the later group three cerebral haemodynamic patterns were considered: 1) Cerebral blood flow within normal limits, in those patients with $AVDO_2$ ranging from 1.3 to 3 µmol/ml, 2) Hyperaemia, in those patients with $AVDO_2$ below 1.3 µmol/ml, and 3) Compensated hypoperfusion, in those cases with $AVDO_2$ above 3.0 µmol/ml.

Neurological outcome was evaluated at three months after injury following the Glasgow Outcome Scale[38]. Patients in the good recovery or moderate disability categories were considered as a good outcome. Patients belonging to the categories severe disability, vegetative state or dead were included in the bad outcome group.

All data are expressed as mean ± standard deviation (SD). Two-tailed Student's t-test, Pearson's correlation test, and linear regression using the least square method were used to compare quantitative variables. Fischer exact test and the Chi-square test were used to compare qualitative variables. The Mann-Whitney U-test was used to compare not normally distributed data. The level of statistical significance was established for $p \leqslant 0.05$.

+ Manufactured by Medical Europe, Milano, Italy.

* Manufactured by Boehringer, Mannheim, Germany.

Results

Age, Sex, and Mechanism of Lesion

The mean age of our series was 31 ± 17 (mean ± SD) years with a range from 17 to 85 years. Twenty-five of the patients were male (95%) and 3 female (5%). Of the 28 patients, 26 (93%) were injured in road traffic accidents (Table 2). All patients were rendered unconscious immediately on impact. All but 4 patients were referred to our hospital having been previously admitted to another center without neurosurgical facilities. Average time interval between injury and admission to our hospital (TIA) was 4.4 ± 3 hours

Table 2. *Demographic Characteristics and Clinical Features of Patients Studied*

	n	%
Cases	28	
Sex		
male	25	95
female	3	5
Cause of injury		
MVA-passenger	22	79
MVA-pedestrian	4	14
gunshot wound	1	4
other	1	4
Glasgow Coma Scale Score		
3-4-5	15	54
6-7-8	13	46
Glasgow Outcome Scale		
GR + MD	10	36
SD + V	6	21
dead	12	43

MVA = Motor-vehicle accident, GR = good recovery, MD = moderate disability, SD = severe disability, V = vegetative state.

Table 3. *Main CT Findings in the Entire Group*

	n	%
Type of lesion		
DBI type I	2	7
DBI type II	11	39
DBI type III	14	50
other	1	4
Basal cisterns and III ventricle		
patent	6	21
partially obliterated	13	46
obliterated	9	32
Subarachnoid haemorrhage		
yes	18	64
no	10	36

(mean ± SD) with a range of 30 minutes to 15 hours. In 19 cases (70%), TIA was less than or equal to 4 hours while in 9 cases the time interval between injury to admission was above 4 hours. Analysis of the post-resuscitation Glasgow Coma Scale Score recorded on admission, showed that fifteen patients (54%) scored equal to or below 6 points and 13 patients scored above 6 points. According to Miller's criteria[46,47,49], 5 patients in this group (18%) had extracranial insults on admission. A clinical summary of these 28 patients is given in Table 2.

Type of Lesion on the CT Scan

The admission CT scans of these 28 patients were reviewed. According to the first CT scan, 27 patients in this series were classified in the group of diffuse brain injury (DBI). The remaining patient who suffered a missile brain injury was included in the group of unilobar injury according to the classification proposed by Levi[42], that considers the extent of cerebral involvement. The 27 patients in the DBI group were subclassified according to the first CT scan in one of the three previously described categories[64,65] (Table 3). Twenty-two of the 28 patients showed a moderate (13 cases) or severe (9 cases) diffuse brain swelling with partial or complete obliteration of the basal cisterns and/or the third ventricle. Subarachnoid haemorrhage was identified in 64% of the patients in the entire group, while intraventricular haemorrhage was detected in only 9 of the 28 patients (32%).

Seven patients presented isolated (3 cases) or multiple small cerebral contusions (4 cases). Three patients had small extradural (1 case) or subdural (2 cases) unilateral collections of blood which were not surgically evacuated.

ICP on Admission and Outcome

In all the above-mentioned 28 cases, ICP was continuously measured over an average period of 6 days. ICP measured at the time of admission was below to 20 mmHg in 17 cases (61%), between 20 and 40 mmHg in 7 cases (25%) and above 40 mmHg in only 4 patients (14%). According to the Glasgow Outcome Scale, 5 of the 28 patients had a good recovery, 5 were included in the moderate disability group, 3 were severely disabled, 3 remained in a vegetative state and 12 died (Table 2). Only 36% of the patients were functional survivors (good recovery and moderate disability). Of the 12 patients who died, 9 died because of early or delayed uncontrollable intracranial hypertension. In the remaining three cases, the cause of death were one or more extracranial complications (sepsis, severe extracranial insults etc.).

Table 4. *Different Variables at the Time of the Study*

	Mean ± SD
HTCT (%)	36.3 ± 5.1
Arterial Hb	12.4 ± 1.8
Arterial pH	7.45 ± 0.1
Arterial PO_2	143 ± 50
Arterial PCO_2	30 ± 5.7
SaO_2	98.7 ± 1.3

Arterial Lactates and AVDL

The average time from accident to the first study was 23.9 ± 9.9 hours. At the moment of the first $AVDO_2$ determination, 23 patients (82%) had normal pupil reactions in both eyes. In 2 patients an impaired unilateral pupillary response and in 3 bilateral non-reactive pupils were found. Different variables at the moment of the study are shown in Table 4.

Arterial lactate was in the entire group 1.99 ± 0.9 µmol/ml. Twenty patients had an increased arterial blood lactate according to the normal values considered for inpatients; that is below 1.25 µmol/ml. Arterial blood lactates in ischaemic and non-ischaemic patients are shown in Table 5. Mean AVDL in the entire group was − 0.241 ± 0.55.

LOI and Ischaemic and Non-Ischaemic Patterns

According to Robertson's criteria, 13 patients (46%) had a calculated LOI ($-AVDL/AVDO_2$) value ≥ 0.08 and therefore an ischaemia/infarction pattern in the immediate 24 hours from the time of the accident.

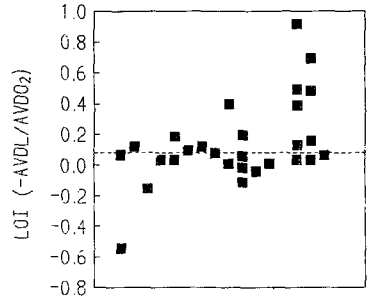

Fig. 1. Lactate Oxygen Index (*LOI*) in the entire study group. Each filled square represents one patient. The dashed line marks the 0.08 level (Ischaemia). For explanation see text

Fifteen patients (54%) had a LOI below 0.08 (Fig. 1). $AVDO_2$ in patients with a LOI above or equal to 0.08 are plotted in Fig. 2. According to Robertson's criteria, 12 of the 15 patients had an estimated normal cerebral blood flow, while in 3 cases the CBF was below the metabolic demands and therefore in a state of compensated hypoperfusion. No patient presented a hyperaemic pattern (Fig. 2). $AVDO_2$ in the ischaemic group is plotted in Fig. 3. Mean $AVDO_2$ in the ischaemic group was 1.91 ± 0.9 while in the non-ischaemic patients $AVDO_2$ was 2.64 ± 0.63 ($p < 0.05$) (Table 5). Table 5 compares metabolic parameters in ischaemic and non-ischaemic patients. An excellent linear relationship was found when plotting AVDL and LOI ($r = 0.82$, $p < 0.001$), the regression line is shown in Fig. 4. The linear relationship in non-ischaemic patients was more intense ($r = 0.94$, $p < 0.001$) than in the ischaemic group ($r = 0.64$, $p = 0.01$).

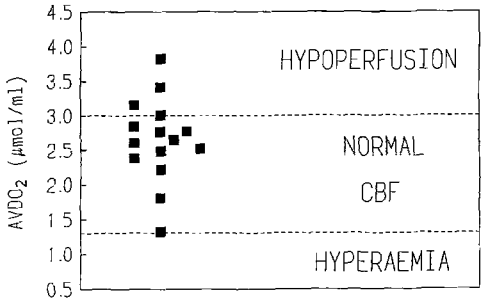

Fig. 2. $AVDO_2$ and estimated cerebral blood flow according to the patterns suggested by Robertson *et al.*[63] in the non-ischaemic group

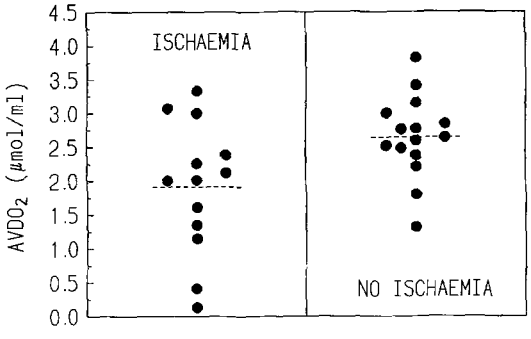

Fig. 3. $AVDO_2$ in ischaemic and non-ischaemic patients. Patients with LOI above or equal to 0.08 are plotted on the left side, and on the right patients with a LOI below 0.08 are represented

Aetiology of Ischaemia and Compensated Hypoperfusion Patterns

The average time from accident to admission was 4.7 ± 4 in the ischaemic group and 3.7 ± 2.5 in non-ischaemic patients, nevertheless, these differences were not significant. Other variables considered important in increasing risk of developing ischaemia are shown in Table 5. Only arterial Hb was significantly different in both groups. The ischaemia score had a mean of 4.3 ± 1.7 in the ischaemic group and 2.7 ± 1.4 in non-ischaemic. These differences were also statistically significant ($p = 0.01$). We divided patients according to their ischaemia score, those who scored 3 or less, and those who scored higher than 3. We found that 9 of the 13 cases (69%) in the ischaemic group and only 3 patients in the non-ischaemic group (20%) scored above 3 points ($p < 0.01$).

In the three patients with a compensated hypoperfusion pattern, the first was probably due to excessive hyperventilation, the second to a low CPP (< 60 mmHg secondary to a low mean arterial blood pressure) and in the third we could not find any risk factor, except that of subarachnoid haemorrhage with which the patient presented on the admission CT scan.

Table 5. *Metabolic Parameters in Ischaemic and Non-Ischaemic Patients*

	Ischaemia n = 13	No Ischaemia n = 15	Significance
Ischaemia score	4.3 ±1.7	2.7 ±1.4	< 0.05
Arterial pO_2	135 ±27	150 ±65	NS
Arterial pCO_2	29.7 ±6.1	29.9 ±5.7	NS
Arterial Lactate	1.87 ±0.8	2.1 ±1.2	NS
Mean CPP (12 hours)	66.5 ±26	75 ±12	NS
Mean ICP	21 ±18	18 ±18	NS
$SatO_2$	98.9 ±0.9	98.5 ±1.5	NS
Arterial Hb (%)	11.7 ±1.8	13.1 ±1.7	< 0.05
Jugular Lactate	2.27 ±0.9	2.0 ±1.1	NS
AVDL	−0.562±0.55	0.037±0.26	< 0.05
$AVDO_2$	1.91 ±0.9	2.64 ±0.6	< 0.05

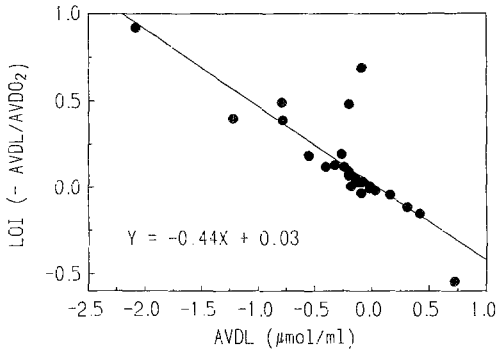

Fig. 4. Linear regression model obtained when plotting LOI and AVDL ($r=0.85$, $p<0.001$). Observe that in spite of the fact that good linear correlation exists, some outliers are present in the plot

Neurological Outcome

Neurological outcome in the entire series is shown in Table 2. In non-ischaemic patients, good results were obtained in 7 cases (47%) and bad outcome in 8 patients (53%). In patients with a LOI index above or equal to 0.08, only 2 (15%) were included in the good recovery or moderate disability groups. The remaining 11 patients had a bad outcome (85%).

Discussion

In spite of significant advances in the last decade, severe head injury continues to have a high mortality and severe morbidity rate. Diffuse axonal injury and ischaemia are the prevalent lesions found at post-mortem studies of PVS after head injury[4-6, 34, 64-66, 68-70], while neuropathologists have shown that ischaemic damage is still a fairly common finding in fatally head-injured patients[1, 5, 30-34]. Ischaemic brain damage can be produced by many factors. Cardiac arrest, breathing abnormalities, epilepsy, reduced regional or global CBF, reduced oxygen content of the blood or vasospasm are the most frequent causative factors[30, 31, 33, 58].

High ICP with a consequently low CPP continues to be the most important single factor producing ischaemia after head injury. Nevertheless, about 30% of patients with a fatal non-missile head injury without high intracranial pressure were shown in Graham's study to have moderate to severe ischaemic damage[32, 33]. The majority of the brain damage in this latter group was secondary to critical reductions in regional cerebral blood flow[32, 33].

Although dynamic changes in CBF and metabolism have been repeatedly reviewed[16, 37, 40, 41, 43, 44, 50, 52, 53, 55], the actual prevalence of true ischaemia in the acute phase of severe head injury has not been well established. Contradictory results have been published by different authors. Prevalence of early ischaemia in diffuse brain lesions is especially obscure because many studies have been performed at different time intervals after injury. Nevertheless, in severe head trauma, it has been clearly established that very low flows, found at any time of the clinical evolution, are related to poor outcome[51].

Overgaard[56] among others, demonstrated that low CBF is quite common in the early phase of acute head injury. Recent CBF studies suggest that patients with a severe head injury[10, 11], and especially those without surgical mass lesions, have a low CBF in the few first hours after injury. Measuring CBF, although technically feasible, is very complicated at the bedside. Also, measuring only CBF can be misleading in some cases in which ischaemia is already present[9, 60, 62, 63]. On the other hand, it has been very well established that when infarction is present, CBF can be normal, high or low without being indicative of ischaemia[9].

Cerebral haemodynamic monitoring is feasible using continuous or intermittent monitoring of $AVDO_2$ or SjO_2 associated or not with CBF measurements. Considerable work in this field has been done over the last seven years[17, 19, 20, 55, 62, 63]. The parameters that are useful when monitoring cerebral oxygenation are the arterio-jugular differences of oxygen ($AVDO_2$) and the cerebral extraction of oxygen (CEO_2)[17-20, 55]. In $AVDO_2$ calculations oxyhaemoglobin is used, while CEO_2 is calculated without using the blood content of oxyhaemoglobin[17, 19, 20].

Two different approaches are possible when using arterio-jugular differences of oxygen in clinical practice. The first would be to use $AVDO_2$ to estimate CBF, this approach being mainly proposed by Robertson *et al.*[60, 62, 63]. The second and most widely applied approach is regarding $AVDO_2$ as representing brain O_2 balance between supply and requirements[17-20, 22, 26], taking into consideration that coupling between CBF and $AVDO_2$ is non-linear[63]. According to the latter approach, when CBF is low relative to the brain's metabolic needs, a wide $AVDO_2$ is obtained (ischaemia)[55]. On the contrary, when CBF is high in relation to metabolism, we get low $AVDO_2$ values which indicate hyperaemia. If the normal coupling between cerebral metabolic ratio of oxygen ($CMRO_2$) and CBF is maintained, then $AVDO_2$ remains constant in the normal range. Nevertheless, this last approach can be mis-

leading in the presence of increased anaerobic metabolism[62, 63].

In traumatic coma, $CMRO_2$ is normally reduced from a normal value of 1.5 μmol/gm/min to values that fluctuate from 0.6 to 1.2 μmol/gm/min[62, 63]. In patients in coma, independent of aetiology, Robertson demonstrated that only 25% of the calculated $CMRO_2$ were below 0.6 μmol/ml[62, 63]. The significant concept put forward by this author, is that in the presence of brain infarction $CMRO_2$ moves out of the expected range and so in this situation $AVDO_2$ is unreliable as an estimate of CBF. In Robertson's series of traumatic and non-traumatic coma, most patients with a CBF measured below 0.20 ml/gm/min would have been misclassified according $AVDO_2$ as having a normal or increased CBF[62, 63]. This fact has also been noted by Baron in non-traumatic ischaemia[9]. Using PET, this author found that in ischaemic stroke, $AVDO_2$ can be high (hyperaemia) in spite of low or normal CBF[9].

Our data are in agreement with those of Robertson *et al.*[62, 63]. When using $AVDO_2$ without taking into consideration AVDL, we found that of the 13 cases with a LOI equal to or above 0.08 (ischaemia/infarction), 3 could have been considered as having hyperaemia (Fig. 3). In patients who we identified as having ischaemia, mean $AVDO_2$ was 1.92 while in the non-ischaemic group arterio-jugular differences of oxygen had a mean of 2.64 ($p < 0.05$). On average, ischaemic patients had $AVDO_2$ significantly lower than patients without increased anaerobic metabolism. This point has also been addressed by Robertson. As a conclusion, Robertson holds that $AVDO_2$ are good estimates of the overall balance between cerebral oxygen supply and demand, except in patients with the ischaemia/infarction patterns[60]. According to our data, in only 54% of our patients $AVDO_2$ could have been used as a guide for estimating CBF.

Measuring $AVDO_2$ and AVDL in clinical practice allows us to find out when significant infarction is evolving in brain injured patients. It has been determined that $CMRO_2$ values below 0.6 μmol/gm/min are exclusively found in those cases with a clear ischaemic injury[62]. According to Robertson, in comatose patients, when ischaemic lesions develop, the increased cerebral lactate production is superimposed on the low normal cerebral lactate production. This increased lactate production creates a clear definition of patients with ischaemic insults. In these circumstances, AVDL becomes more negative.

Lactates can be produced or consumed by the brain. In general, a small quantity of lactates are given out by the brain to the blood. It is generally accepted that the arterial level of lactates does not control the rate of utilization by the brain. An interesting finding in our series are the increased arterial lactate levels which we found in 71% of the entire group. Arterial lactates have been found increased after experimental severe head injury[36]. These increases in blood lactates are probably due to augmented circulating cathecholamines in the early hours after impact and to peripheral ischaemia later on[36, 61].

Delay in the process of transfer from the accident to the referral hospital or from this point to the hospital with neurosurgical facilities, are potential factors that increase the number of secondary insults and, therefore, brain ischaemia. In spite of some improvement in the last 3 years, time from injury to admission in our hospital continues to be lengthy. Although not statistically significant, the average time from injury to admission was 1 hour longer in patients with increased anaerobic metabolism than in those without ischaemia. Graham observed that ischaemic brain damage frequently occurred after patients came under medical care[31]. A high prevalence of ischaemia/infarction within the first 24 hours after impact was found in our series (46%). Fifty-four per cent of patients in our study scored equal to or below 5 on admission, showing a very severe DBI. This point could result in bias in our series. To differentiate between intrahospital and prehospital causes of ischaemia is very difficult because global or regional brain ischaemia can occur prior to admission to the hospital or in periods immediately after injury, being sometimes difficult to detect or document.

In ischaemic brain damage, differentiating between early and delayed ischaemic lesions is necessary[13]. Some events constantly found in animal models very early after impact are important in developing brain ischaemia. However, information about the changes in ICP, CPP and other important parameters immediately after head injury are only available in laboratory models. Although animal models of severe head injury have demonstrated that some factors can be responsible for early ischaemia following brain injury, data from different experimental studies are sometimes misleading due to the varying severity of the trauma and different head injury devices employed. Using a modification of the fluid percussion model, Pfenninger has demonstrated that ICP increases in head injured piglets immediately after trauma, reaching the maximum level 1 minute after impact[57]. At the same time, a low CPP

and low CBF secondary to increased cerebral vascular resistance are immediately produced. In this study, high ICP and low CPP are still recorded two hours after trauma[57]. These and other data support the fact that the cerebral circulation is critically affected in severe head injury very early after impact.

Posttraumatic apnea and respiratory depression has been found in both clinical and experimental head injuries. In the ventilated cat, fluid percussion models at 3.2 atm do not significantly affect CBF or $CMRO_2$ in the immediate period after injury[8, 71]. Nevertheless, when a period of hypoventilation is added to the cats, a shift from aerobic to anaerobic metabolism is observed[8, 71]. Hypoventilation after head injury seems to blunt CBF increases in response to hypoxaemia and therefore is responsible of increasing anaerobic metabolism[8].

In our series, all but one patients had a non-missile diffuse brain injury while 61% of the entire group had no increased ICP on admission. The chief histopathological lesion in these patients is, in the majority of cases, an acceleration induced diffuse axonal injury of varying severity[65]. Diffuse axonal injury has been reproduced in subhuman primates using non-impact angular acceleration capable of producing graded injuries from subconcussive to instantaneously lethal. Gennarelli unequivocally demonstrated in experimental controlled acceleration injury that respiratory changes are produced, ranging from irregular gasping to transient apnea to permanent respiratory arrest[2, 23, 25, 65]. Intense bradycardia was also found in these animals[23–25]. Adams, analyzing the same group of animals, demonstrated early hypoxic brain damage located in the neocortex and Ammon's horn of those primates with head injury of intermediate severity in whom high ICP was not an important factor[2, 3].

There are several factors that favor the development of ischaemia. To compare risk factors between ischaemic and non-ischaemic patients, we devised the IS. IS was significantly higher (4.3 ± 1.7) in patients with ischaemia compared to patients without increased anaerobic metabolism (2.7 ± 1.4). This fact points out that in these patients ischaemia is related to multiple factors. In an analysis of different variables, we could find that apart from IS only haemoglobin was significantly lower in patients with an increased anaerobic metabolism.

Obrist's clinical studies have demonstrated that low CBF is quite common in the acute phase after severe head injury[55]. Nevertheless, in the same group of patients only a few cases had wide $AVDO_2$ suggesting ischaemia[55]. This and other studies suggest that measuring $AVDO_2/AVDL$ is perhaps better and more accurate from a physiological point of view than measuring only CBF by conventional methods as Xenon-133[9]. Baron has shown that measuring only CBF can be misleading in the presence of brain infarction[9]. However, some drawbacks can affect the reliability of $AVDO_2/AVDL$ in brain haemodynamic monitoring. $AVDO_2$ are estimates of hemispheric values, therefore, hypoperfused and hyperperfused regions can coexist giving mean values close to normal[13]. Nevertheless, in these patients increased AVDL can be detected in order to find out the reliability and sensitivity of AVDL in detecting brain infarction, clinical studies are in progress in our center.

From a clinical point of view, a significant point to take into account, is that compensated hypoperfusion patterns are treatable and potentially reversible situations. Robertson has also shown that in some cases of increased anaerobic metabolism, the ischaemia can be reversed. Our sequential studies suggest that patients with an increased LOI can reverse to normal aerobic metabolism in certain circumstances (Sahuquillo *et al.*, in press).

Bullock has stated that for a monitoring technique to be useful it must be performed frequently and improve patient management[14]. Monitoring $AVDO_2/AVDL$ is simple and has a small rate of complications, when used appropriately. The most important drawback for haemodynamic monitoring through $AVDO_2$ is the problem of the representativeness of $AVDO_2$ when blood samples are extracted from one jugular vein. In diffuse brain injuries, $AVDO_2$ are good estimates of brain metabolism, nevertheless, how this method can be extended to patients with a focal lesion has yet to be worked out. A second drawback is the fact that for a single arteriovenous difference to be interpretable, the venous blood draining in the brain must be in equilibrium with the brain tissue[7]. This equilibrium has been found for oxygen[7], although some doubts have been raised by some authors about lactate. Alexander states that when CMRL is not increased, a disequilibrium between brain and venous blood could be the reason, but according to the same author, increased CMRL indicates increased anaerobic metabolism[7].

Intermittent determinations of AVDL with continuous monitoring of jugular oxygen saturation might be a good way to monitor brain haemodynamics. It

could be useful in detecting early ischaemia and in monitoring treatment and especially mechanical ventilation. Excessive hyperventilation was responsible for compensated hypoperfusion in one case in our series. Hyperventilation is widely used as a first or second step in treatment of increased ICP in severely head injured patients. Extreme hypocarpia below 20 mmHg can produce an increase in anaerobic metabolism[7].

We believe that monitoring haemodynamic variables are essential very early after head injury. Application of these techniques to some brain treatments could be helpful. In spite of the fact that our data detect a high prevalence of early ischaemia, to draw general conclusions is difficult taking into account that the number of cases in our series is small. An important goal in measuring anaerobic metabolism in the early phase of acute head injury is to identify patients that might benefit from being treated with several agents that have been effective in treating ischaemia experimentally. It might be possible that in the future agents such as nimodipine, THAM, lazaroids or other neuroprotective agents could be employed in patients with a DBI to prevent or reverse brain ischaemia. This point is now open to discussion and awaits further studies.

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