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Arterio-Jugular Differences of Oxygen ($AVDO_2$) for Bedside Assessment of CO_2-Reactivity and Autoregulation in the Acute Phase of Severe Head Injury

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Summary

Autoregulation and CO_2-reactivity can be impaired independently of each other in many brain insults, the so-called 'dissociated vasoparalysis'. The theoretical combination of preserved CO_2-reactivity and impaired or abolished autoregulation can have many clinical implications in the daily management of brain injured patients. To optimize their treatment, a bedside assessment of autoregulation and CO_2-reactivity is desirable. When cerebral metabolic rate of oxygen is constant, changes in arterio-jugular differences of oxygen ($AVDO_2$) reflect changes in CBF. In these situations relative changes in $AVDO_2$ can be viewed as inverse changes in CBF and used as an evaluation method of CO_2-reactivity and autoregulation. In 39 consecutive severe head injury patients with a mean age of 28 ± 17 years and a diffuse brain injury, cerebrovascular response to changes in pCO_2 was tested in the acute phase after injury (18 ± 8 hours). In 28 of those cases autoregulation was also assessed. A relative CBF value ($1/AVDO_2$) was calculated from baseline $AVDO_2$ and was expressed as 100%. Changes in $1/AVDO_2$ after inducing pCO_2 changes give a good estimate of changes in global CBF. Two different indexes were calculated for CO_2-reactivity: 1) absolute CO_2-reactivity (CO_2R_{ABS}) and 2) percentage reactivity ($CO_2R\%$). $CO_2R\%$ was used to separate patients with impaired/abolished CO_2-reactivity from those with preserved CO_2-reactivity. Patients with $CO_2R\%$ above 1% were considered in the intact CO_2-reactivity group and patients in whom $CO_2R\%$ was below or equal to 1% were included in the impaired/abolished CO_2-reactivity group. Only five cases (12.8%) presented an impaired/abolished CO_2-reactivity. $AVDO_2$ response to induced hypertension was studied in a subset of 28 patients. Phenylephrine was used to increase MABP about 25%. All $AVDO_2$ values were corrected for changes in pCO_2. Patients with changes in $1/AVDO_2$ less than or equal to 20% were included in the intact autoregulation group. Patients with estimated CBF changes above 20% were classified as having an impaired autoregulation (impaired/abolished). In 12 patients (43%) autoregulation was intact. In the remaining 16 patients (57%) autoregulation was impaired. Of the 28 cases, CO_2-reactivity was impaired in only five cases. All patients with an impaired CO_2-reactivity also had an impaired autoregulation. Monitoring relative changes in $AVDO_2$ permits a reliable study of CO_2-reactivity and autoregulation at the bedside. Introducing these variables into the day-to-day management should be considered in treatment protocols.

Keywords: Head injury; autoregulation; CO_2-reactivity; arterio-jugular differences of oxygen.

Introduction

In spite of significant advances in prehospital care and early aggressive management, increased intracranial pressure (ICP) continues to be the main cause of mortality and morbidity in severe head injury patients. In the Traumatic Coma Data Bank's recent published results, a prevalence of 72% of high ICP has been reported in patients with a Glasgow coma scale score of eight or less following non-surgical resuscitation [37]. Although multiple factors can lead to an increase of brain volume in the early stages of head trauma, vascular mechanisms seem to predominate over non-vascular ones and an increase of the cerebral blood volume (CBV) is the main recognized cause of high ICP [38, 40, 44–47].

Because of the unique characteristics of the cerebral circulation, i.e., the absence of precapillary sphincters, resistance across the cerebrovascular bed and so CBF is mainly regulated at the level of the arterial and arteriolar segments [19]. Impairment of autoregulatory mechanisms and CO_2-reactivity of the cerebrovascular bed is quite common in the acute phase of the severe head injured patient and play an important role in the physiopathology of the increased CBV and high ICP [8, 29, 35, 36, 53,66].

It has been shown both clinically and in experi-

mental models, that autoregulation and CO_2-reactivity can be impaired independently of each other in many brain insults (tumours, hypoxia, seizures etc.), the so-called 'dissociated vasoparalysis' [34, 55, 56, 65]. In addition, it has been suggested that occasionally, partial or complete restoration of normal autoregulation can be brought about by moderate hypocapnia [55]. Harper, among others, has shown in animal experiments that hypercapnia can induce a right-hand shift of the autoregulatory curve [28, 55]. Although less studied in head injury, this dissociated paralysis has been observed in other clinical situations in which the brain is threatened such as in non-pulsatile cardiopulmonary bypass [34].

The theoretical combination of preserved CO_2-reactivity and impaired or abolished autoregulation can have many clinical implications in the daily management of brain injured patients. To optimize their treatment, a bedside assessment of autoregulation and CO_2-reactivity is desirable. Increasing BP in an attempt to improve cerebral perfusion pressure could be of no use and even hazardous in non-autoregulating patients because of the increase of CBV and the overload of the cerebrovascular capillary bed. Manipulation of CBV through changes in pCO_2 is a widely used therapeutic measure to control high ICP in head injured patients. However, hyperventilation may decrease CBF to the limit of ischaemia in areas with preserved CO_2-reactivity and simultaneously increase CBF in areas with impaired or abolished CO_2-reactivity (inverse steal phenomenon) [22].

Although technically possible, accurate evaluation of CO_2-reactivity and autoregulation requires complicated and awkward methods of measuring CBF (^{133}Xe, Nitrous Oxide etc.), which are unsatisfactory in the daily bedside care of head injury patients [48, 50, 51, 53]. Although the fact that changes in oxyhaemoglobin saturation in the jugular bulb reflect the coupling between CBF and $CMRO_2$ has been known since Kety and Schmidt's studies [30, 33], their use in the routine management of head injured patients was not introduced until Cruz's *et al.* pioneer contribution [11, 14, 16]. In spite of some unresolved methodological problems, monitoring haemodynamic parameters through a reverse catheter with its tip in the jugular bulb is an easy way of monitoring brain metabolism/CBF coupling and in some cases of estimating CBF [9, 10, 12–15, 58, 59]. If we accept the fact that $CMRO_2$ is constant during the test, CBF is directly proportional to the reciprocal of $AVDO_2$ ($1/AVDO_2$) [12, 13, 15, 58, 59, 62]. Therefore, using $AVDO_2$ as a reliable estimate of CBF changes is possible. This approach has been widely used by different authors and recently put forward as an accepted and reliable method for studying the effects of drugs on autoregulation [54, 60, 61]. $AVDO_2$ or CEO_2 (arterial minus jugular oxygen saturation) can be equally used to monitor CBF changes. Our aims in this paper are to use relative changes in $AVDO_2$ after manipulations of mean BP and arterial pCO_2 to assess autoregulation and CO_2-reactivity in severe head injury patients.

Patients and Methods

In 39 consecutive severe head injury patients (post-resuscitation prehospital or admission Glasgow coma scale score ≤ 8) with a diffuse brain injury, cerebrovascular response to changes in pCO_2 was tested in the early hours after injury. Diffuse brain injury was considered in all the patients with midline shift below 3 mm and without measured focal lesions above 25 ml in the admission CT scan. In 28 of these cases autoregulation was also assessed. The protocol used in our study was reviewed and approved by the Ethics committee of the Vall d'Hebron University Hospitals.

As a rule, on admission to the emergency room, patients with a severe head injury are evaluated by anaesthesiology, orthopaedic, ICU and neurosurgical staff and multidisciplinary resuscitative measures are taken. 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 and/or a volume above 25 ml are usually evacuated. The intracranial epidural pressure or brain tissue pressure is continuously monitored in all patients with a GCS score below or equal to eight. In all but four cases in this study brain tissue pressure was monitored using an intraparenchymatous Camino device (Model 110-4B manufactured by Camino Laboratories, San Diego, CA, USA). In the remaining two patients, an extradural device was used (Ladd Research Industries, Inc, Burlington, Vermont).

Once in the ICU, patients are positioned and maintained at a head elevation of approximately 30°. Patients with increased intracranial pressure (ICP), above 20 mm Hg, are initially treated with mannitol and mild hyperventilation (3.5–4.5 Kpa). In those cases with refractory increases of ICP, barbiturates are initiated. Routine medication includes phenytoin, morphine, midazolam, furosemide, and pancuronium. In all cases mean arterial blood pressure (MABP), mean ICP and cerebral perfusion pressure (CPP) are routinely monitored.

$AVDO_2$ Measurements

Immediately after admission a radial artery is canalized in each patient and a 14G catheter inserted percutaneously in the internal jugular bulb using the technique described by Goetting *et al.* or occasionally the so-called 'very high approach' to the jugular vein [24–26, 43]. The catheter is placed, whenever possible, on the right side. X-ray verification of the catheter position is obtained in all patients before obtaining jugular blood samples. Optimal localization of the catheter tip is above the lower border of the posterior arch of C1. In a recent study Bankier *et al.* have suggested that a

correctly positioned catheter tip should lie cranial to a line that connects the tips of the mastoid processes in an anteroposterior radiograph, with a catheter tip-to-line distance averaging 20% of the distance between the tips of the mastoid processes [5]. In our study catheter tips above the arch of C1 were considered adequately placed. Those cases with an inappropriate positioning of the reverse jugular catheter were excluded. Arterial and jugular blood samples were obtained simultaneously, at least twice during the first 24 hours after injury. In some patients continuous monitoring of SjO_2 through a 5.5 Fr fibreoptic catheter and an Oximetrix-3 monitor (Opticath, 5.5 Fr and Oximetrix-3 monitor supplied by Abbott Laboratories, S.A., Madrid) was performed. In those cases in whom the Oximetrix-3 was used, jugular blood samples and not the measurements of the oximeter were used to calculate $AVDO_2$. Blood gases were analysed on a BGM Instrumentation Laboratory analyser, model 1312 (Supplied by Medical Europe, Milan, Italy).

Arterio-jugular differences of oxygen ($AVDO_2$) were calculated by using the following equation: $AVDO_2 = 1.34 \times Hb\ [SaO_2 - SjO_2)/100]$, where Hb is arterial oxyhaemoglobin content in gr/dl and SaO_2 and SjO_2 are, respectively, the percentage of saturated oxyhaemoglobin in the arterial and jugular blood. $AVDO_2$ were expressed in µmol/millilitre.

CO_2-Reactivity Studies

To test CO_2-reactivity, and as a first step, arterial and jugular blood samples were extracted to establish baseline values for pCO_2 (pCO_{2B}) arterial pO_2, oxyhaemoglobin saturation in the jugular bulb ($SJO2_B$), arterial oxyhaemoglobin saturation (SaO_2), haemoglobin content (Hb) and basal arterio-jugular differences of oxygen ($AVDO_{2B}$). Basal intracranial pressure (ICP_B) and mean arterial blood pressure (MABP) were also determined. These values were used as a reference for the following manipulations of arterial pCO_2. As a second step, manipulations in the ventilator settings were made to change the basal arterial pCO_2. The goals in changing ventilator parameters were to increase or decrease arterial pCO_2 toward the 'normoventilation range'. To simplify these tests, and to avoid unnecessary ventilator manipulations, in those patients with a basal pCO_2 below 40 mm Hg, the ventilator settings were manipulated to increase the arterial pCO_2 while, in those with pCO_2 above or equal to 40 mm Hg, the manipulations were directed to reduce arterial pCO_2. The mean absolute change in arterial pCO_2 in the entire group was 4.4 ± 2.3 mm Hg (mean ± SD). After 10–15 minutes of the ventilator manipulations $AVDO_2$ and all the above-mentioned parameters were recalculated. $AVDO_2$ values after ventilator manipulation were expressed as $AVDO_{2H}$.

Assuming a constant $CMRO_2$ during the test, changes in $AVDO_2$ reflect inverse changes in CBF. A relative CBF value ($1/AVDO_{2B}$) was calculated from baseline $AVDO_2$ and was expressed as 100% [54, 61]. Changes in $1/AVDO_2$ after pCO_2 manipulation give a good estimate of changes in global CBF [54, 61].

Two different indexes were calculated for CO_2-reactivity: 1) Absolute CO_2-reactivity (CO_2R_{ABS}) and 2) percentage reactivity ($CO_2R\%$) [1, 17]. Absolute reactivity refers to the absolute change of $AVDO_2$ per mm Hg change in the arterial pCO_2 and was calculated as the change in $AVDO_2$ divided by the measured change in pCO_2: Delta $AVDO_2$/Delta pCO_2 [17]. The results were expressed as µmol/mm Hg pCO_2. Percentage reactivity was calculated as the percent increase or decrease of estimated CBF ($1/AVDO_2$) per mm Hg change in pCO_2. This index was calculated according to the following equation: $[(1/AVDO_{2H}-1/AVDO_{2B})/1/AVDO_{2B}] \times 100$. The resulting percent change in estimated CBF was then divided by the delta of pCO_2 and the absolute value was considered. In this study changes with hyper- and hypoventilation were placed together. A third index, pressure reactivity coefficient to changes in arterial pCO_2 (PR_{CO2}) was calculated as proposed by Marmarou and Wachi i.e., the change in steady state ICP per torr change in arterial pCO_2 [39]. To avoid contamination of the results by hypoxaemia-induced changes in CBF, patients with any pO_2 value below 60 mm Hg were excluded. Any patient with changes in MABP above 10 mm Hg was also excluded to avoid superimposing changes in $AVDO_2$ provoked by autoregulatory mechanisms.

Testing Autoregulation

Changes in global CBF were estimated from repeated measurements of $1/AVDO_2$ [61]. To avoid oligaemic insults, only the $AVDO_2$ response to induced hypertension was studied in a subset of 28 patients. In all of them CO_2-reactivity had been studied previously. In every patient, and to avoid influences of pCO_2 in the autoregulatory response, manipulations of the ventilator settings were made when necessary to obtain a baseline pCO_2 in the normoventilation range (35–45 mm Hg). In each case, direct measurement of MABP was taken through a catheter introduced into the radial artery. In haemodynamic stable patients, phenylephrine (Neosynephrine, Sanofi-Winthrop, Brussels, Belgium) was used to increase MABP by about 25% [52]. Usually 10 mg of intravenous infusion of phenylephrine in 500 ml of saline solution was used to increase the MABP gradually. Mean increase in BP in the entire group was 25 ± 9 mm Hg (mean ± SD). Arterial and jugular blood samples to calculate $AVDO_2$ were obtained before (Baseline) and after a steady state of MABP was achieved. All $AVDO_2$ values were corrected for changes in pCO_2 using the absolute CO_2-reactivity (CO_2R_{ABS}) index calculated in the previous study. Corrected changes were used in the calculations of the autoregulatory response.

Theoretically, changes in $1/AVDO_2$ should be negligible if the autoregulation is intact and therefore, CBF does not change when increasing MABP. The percent change of $1/AVDO_2$ relative to the resting value (corrected for pCO_2) was calculated according to the following equation:

$\%(1/AVDO_2) = [(1/AVDO_2B\text{-}1/AVDO_2H)/1/AVDO_2B]*100$,

where $AVDO_2B$ are the basal arterio-jugular differences of oxygen and $AVDO_2H$ the arterio-jugular differences of oxygen after raising MABP with phenylephrine. Additionally, and in every patient, pressure reactivity to induced hypertension (PRIH) was calculated as the ratio between the change in steady state ICP per torr change in mm Hg arterial MABP. According to $\%(1/AVDO_2)$, and following the values exposed below, patients were classified as those with preserved autoregulation and those with impaired/abolished cerebrovascular response to increased BP.

Normal Range

CO_2-reactivity. Some variability exists in the literature about the 'normal' range for CO_2-reactivity. Different studies using measurements of CBF, have reported values for relative CO_2-reactivity ($CO_2R\%$) ranging from 1–4% for head injuries [23, 36, 53]. $CO_2R\%$ was used to separate patients with impaired/abolished CO_2-reactivity from those with preserved CO_2-reactivity. Nevertheless, in our study, normal range was calculated from studies done in awake or anaesthetized patients without intracranial pathol-

ogy. From different published studies the mean percent change of CBF per mm Hg pCO_2 in normal awake volunteers ranged from 1.8 to 2.3 [31, 32, 41, 42]. The lower 2.5 percentile varied from different published studies because of the reduced number of cases studied. The lower 2.5 percentile in the McHenry study was 0.8 [41] and 1.2 in the Kety study [31]. Therefore, patients with $CO_2R\%$ above 1% were considered in the intact CO_2-reactivity group and patients in whom $CO_2R\%$ was below or equal to 1% were included in the impaired/abolished CO_2-reactivity group.

Autoregulation

If autoregulation is intact, very small changes in CBF are expected when increasing MABP within the limits of the autoregulatory curve. According to Enevoldsen and Jensen's criteria [22], patients with changes in $1/AVDO_2$ less than or equal to 20% were included in the intact autoregulation group. Patients with estimated CBF changes ($1/AVDO_2$) above 20% were classified as having an impaired autoregulation (impaired/abolished).

Statistical Analysis

The assumption that data came from a normal distribution was tested using the Shapiro-Wilks test [63]. In normal distributed data, the mean ± SD was used to summarize variables [4]. In skewed samples, as in most of CO_2-reactivity and autoregulation coefficients, the median and the 2.5 and 97.5 percentiles were calculated. To quantify correlation between normally distributed data the Pearson product moment correlation coefficient (r) was calculated. Regression analysis was done in some continuous variables using the least square method. Statistical analysis was carried out with the SAS package version 6.08 (Supplied by SAS Institute Inc, Cary, NC, USA). The level of statistical significance was established at 0.05.

Results

Description of the Samples and CT Scan Findings

The mean age in our series was 28 ± 16.7 years (mean ± SD) with a range from 14 to 85 years. Thirthy-four of the patients were male (87%) and five females (17%). Of the 39 patients, 31 (80%) had been injured in a road traffic accident. Analysis of the post-resuscitation Glasgow coma scale score recorded on admission, showed that 18 patients (46%) scored equal to or below six points and 21 patients (54%) scored above six and below eight points. Basal cisterns were compressed in 12 cases (31%) and absent in 11 (28%). Subarachnoid haemorrhage was visible in 16 cases. Six patients presented isolated (4 cases) or multiple small cerebral contusions (2 cases). In four cases small extradural (2 cases) or subdural (2 cases) unilateral collections of blood were detected that were not surgically evacuated.

CO_2-Reactivity

In the entire group, CO_2-reactivity was tested within a mean of 18.1 ± 7.5 hours after injury. CO_2-reactivity was tested in 9 cases within the first 12 hours of the accident. In 25 cases the time from injury to study was above 12 and below 24 and in 5 cases above 24 and below 39 hours. Thirteen additional patients were tested but discarded from the study. Of these 13, nine were excluded because alterations in MABP above 10 mm Hg occurred when changing the ventilator settings and could potentially alter the results due to superimposed changes of autoregulatory mechanisms. Four additional cases were also excluded because of unexpected and paradoxical changes in $AVDO_2$ with changes in pCO_2. Basal haemodynamic variables in this group are summarized in Table 1. Fifteen of the 39 cases (39%) had a basal ICP above or equal to 20 mm Hg at the moment of testing CO_2-reactivity. Of the 39 cases, arterial pCO_2 was increased in 25 and decreased in 14. The mean absolute induced change in arterial pCO_2 was 4.6 ± 2.4 mm Hg with a maximum change of 11.3 mm Hg. In Fig. 1 the observed values of $AVDO_2$ are plotted against basal arterial pCO_2. A good linear relationship was found between both variables with an intercept of 4.0 ($p < 0.0001$). Nevertheless, important inter-individual variations and a non-constant variance was observed in the linear regression analysis.

Table 1. *Summary of Basal Variables in CO_2-Reactivity Group ($n = 39$)*

	Mean	STD	Min	Max
Haemoglobin (g/dl)	12.5	1.2	9.4	14.7
Arterial pO_2 (mm Hg)	142.8	43.7	68.9	300.9
Arterial pCO_2	31.2	5.4	22.7	44.5
$SatO_2$ (%)	98.7	1.3	92.6	99.9
Jugular pO_2 (mm Hg)	36.0	6.7	25.0	55.0
Jugular pCO_2 (mm Hg)	40.2	5.9	30.0	55.3
SjO_2 (%)	66.7	8.8	50.9	81.4
MABP (mm Hg)	91.9	13.3	71.3	122.7
ICP (mm Hg)	17.3	9.8	1.0	42.0

STD standard deviation, *Min* minimum value, *Max* maximum value.

Mean change in estimated CBF with arterial pCO_2 manipulations was 22% although a wide range was obtained (0.35 to 64%). In the entire group the median of the CO_2R_{ABS} was 0.1 µmol/mm Hg pCO_2 with a lower 2.5 percentile of 0.001. The $CO_2R\%$ has a median of 4.4% with a lower 2.5 percentile of 0.06 and a higher 97.5 percentile of 29.3% change in estimated CBF per mm Hg change in arterial pCO_2. According to the above-mentioned criteria, only five

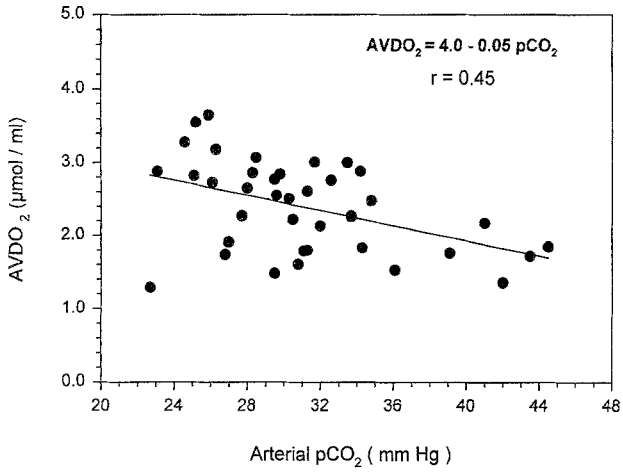

Fig. 1. Basal arterial pCO_2 plotted against basal $AVDO_2$ (µmol/ml). In spite of inter-individual differences, a good linear relationship between both variables was found

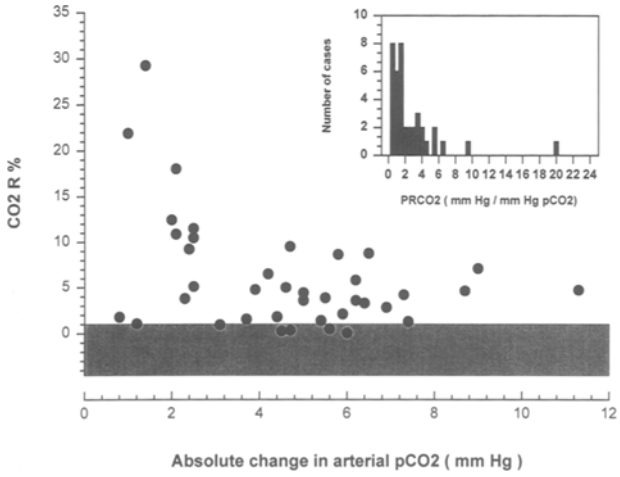

Fig. 2. Absolute change in arterial pCO_2 plotted against $CO_2R\%$. The grey box defines the zone of impaired/abolished CO_2-reactivity according to the criteria described in the text. Observe the lack of correlation of the magnitude of change in pCO_2 during the test and CO_2-reactivity. Only five cases had an impaired autoregulation according to the established 1% limit. Inset: Histogram showing pressure reactivity index ($PRCO_2$) in the entire group

cases (12.8%) presented an impaired/abolished CO_2-reactivity. Of the five patients with an impaired/abolished CO_2-reactivity, four had a Glasgow coma score below five on admission. Three of these patients died, one case was severely disabled and one case was in a persistent vegetative state three months after injury. The reduced number of cases ruled out statistical analysis of the outcome.

The median of $PRCO_2$ was 1.2 mm Hg ICP/mm Hg pCO_2 in the entire group. The maximum absolute

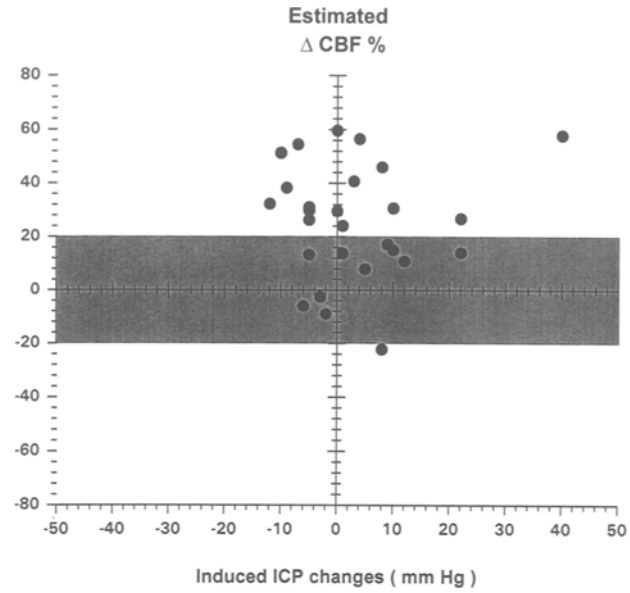

Fig. 3. Induced ICP changes plotted against increases in estimated CBF during the autoregulation tests. The limits of preserved autoregulation are marked by the grey box

change was of 20 mm Hg per mm Hg change in arterial pCO_2. $CO_2R\%$ is plotted against absolute change in arterial pCO_2 in Fig. 2.

Autoregulation

In thirty-five of the 39 patients autoregulation was also tested. Of the 35 cases studied, five were excluded because changes in pCO_2 during the autoregulation test were above 2.5 mm Hg and another two because of paradoxical decreases of mean BP with phenylephrine in haemodynamically unstable patients. The mean change in MABP in this subgroup of 28 cases was 26 ± 9.5 mm Hg. In 12 patients (43%) changes in estimated CBF were below the 20% margin defined to consider autoregulation as intact. Of the remaining 16 patients (57%) autoregulation was impaired. One patient with an induced decrease of –22% of estimated CBF when increasing MABP was included in the 'intact' autoregulation group.

In 15 of the 28 cases ICP increased when increasing BP (Fig. 3). Nevertheless, in all but two cases (10.7%) the net result was an increase of the CPP (Fig. 4). The mean increase in CPP with the induced increase in MABP was 24.2 ± 11 mm Hg (range 1.30–44.6 mm Hg). Of the 15 cases in whom ICP rose with increased MABP, in 8 autoregulation was intact according to the above-mentioned criteria and in 7

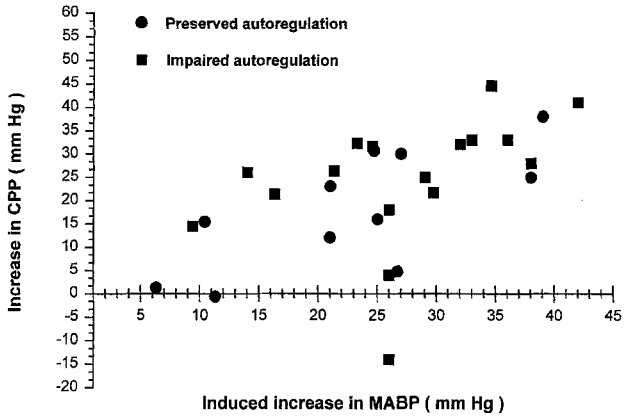

Fig. 4. Phenylephrine-induced increase in MABP plotted against the increase in CPP in patients with impaired autoregulation (square symbols) and preserved autoregulation (black dot symbols). In patients in whom CPP increased, a linear relationship between MABP and CPP was observed (r = 0.65)

autoregulation was impaired/abolished. Of the 28 cases in whom autoregulation was tested, CO_2-reactivity was impaired in five. All patients with an impaired CO_2-reactivity also had an impaired autoregulation.

Discussion

Using $AVDO_2$ in testing CO_2-reactivity assumes that $CMRO_2$ is not altered by changes in arterial pCO_2. This point has been validated by many studies in awake and anaesthetised man either with hyper- and hypoventilation [6, 41, 42, 62, 67]. In our study, a good inverse linear relationship was found between basal $AVDO_2$ and arterial pCO_2. This is in agreement with the relationships found by many authors between pCO_2 and CBF. The relationships between pCO_2 and CBF follow an asymmetric sigmoid curve [57] and are nearly lineal when pCO_2 ranges from 20 to 90 torr [2, 27, 57]. Above and below this range, the responsiveness of the cerebrovascular tree is reduced [27, 57]. In the monkey, Grubb *et al.* found that for each torr change in pCO_2 a corresponding change of 1.8 ml/100 mg/min of CBF was produced [27]. In monkeys, the range of response of CBF to pCO_2 varies from a minimum flow of 45% of normal to a maximum flow of 240% of normal [57]. Nevertheless, the exact type of relationship between pCO_2 and CBF is still under discussion. Some authors believe the relation is lineal, others sigmoid and others hyperbolic and could change depending on the state of the patients studied (anaesthetized versus awake) [2]. CO_2-reactivity has also been shown to be variable in the same individual at different times [62]. Different tests of hypoventilation in the same group of people show similar but not identical responses [62]. Shapiro *et al.* emphasized that clinical tests based on a single CBF response to CO_2 must be interpreted with caution because of this variability [62]. Due to this, we think it is better to speak of preserved versus impaired instead of normal versus abnormal CO_2-reactivity.

The 'Normal Range' for Autoregulation and CO_2-Reactivity

Different criteria have been suggested to consider CO_2-reactivity and autoregulation intact or impaired. Usually authors have not justified why those limits were used. The data we have used for CO_2-reactivity were extracted from the pooled results of different studies. For autoregulation Enevoldsen criteria were used. According to our above-mentioned criteria, only 12.8% of the patients studied presented an impaired CO_2-reactivity in the first 24 hours after injury. The median $CO_2R\%$ in our group (4.4%) was similar to the correction factor suggested by some authors to compare different groups of patients at different arterial pCO_2 levels [53, 61]. However, the wide variability in $CO_2R\%$ in our study suggests that a better approach would be to use individualized $CO_2R\%$ to avoid unrealistic results.

Some of our patients presented a $CO_2R\%$ above 10% and could be incorrectly classified as 'hyper-reactive'. Nevertheless, the relationships between CBF and $AVDO_2$ are nonlinear and follow an exponential pattern [59]. Because of this, patients with a low CBF can have relatively higher changes in $AVDO_2$ and be wrongly considered as hyper-reactive. So, when studying CO_2-reactivity it is possible to say that reactivity is impaired or normal but unfeasible to say that it is above the normal range. Additional caution should be exercised in head injured patients who present decreased CO_2-reactivity, because of the multiple drug treatment these patients usually receive. The effects of any of the drugs regularly used in this group of patients are in some cases debatable. Barbiturates, indomethacin and propanolol among other drugs, can influence the CO_2-reactivity of the cerebrovascular bed [20].

CO_2-Reactivity and the Management of Head Injuries

Preserved CO_2-reactivity in head injury means that aggressive hyperventilation should be avoided. If we

hyperventilate patients with a normal CO_2-reactivity it is possible to induce a shift to anaerobic metabolism. Allen *et al.* in a retrospective study of 14 patients hyperventilated to pCO_2 of 25–30 mm Hg, found that 7 had a high extraction rate of oxygen indicating ischaemia [3]. Continuous or intermittent monitoring of SjO_2, the so-called 'optimized hyperventilation' is useful in controlling the adequacy of CBF during hyperventilation and allows us to avoid ischaemic levels of arterial pCO_2.

Changes in pCO_2 produce changes in CBV and therefore, changes in ICP when patients are shifted to the right in the pressure-volume curve. In our series, changes in arterial pCO_2 lead to absolute changes in ICP of 1.2 mm Hg per mm Hg of change in pCO_2 with most of the patients having values below 4 mm Hg/mm Hg pCO_2. Our results are somewhat higher than those observed by Marmarou and Wachi in the first 24 hours after head injury (0.6 mm Hg per torr change in pCO_2) [39]. These differences can be explained by different patient selection (diffuse brain injuries in our group) or because of the different ICP levels in both series. Because ICP response to arterial pCO_2 changes is essentially a volume response of the intracranial space, it is highly dependent on the compliance at the time of the test and therefore not entirely comparable when patients with different ICP levels are considered.

Preserved versus Intact Autoregulation

When testing autoregulation, an important factor to consider is that between autoregulatory limits CBF is relatively, but not absolutely constant [18, 21]. Because of this, a ± 20% limit was selected according to Enevoldsen's criteria [22]. However, autoregulation limits have not been clearly established and therefore our results should be analysed with caution. In some cases in our series, spontaneous changes in pCO_2 could be induced by changes in MABP when testing autoregulation [61]. Therefore, correcting each patient's autoregulation results in changes in arterial pCO_2 with its own individual CO_2-reactivity and is important for improving accuracy of data. In our study the patient's CO_2-reactivity was used to control for changes in arterial pCO_2.

Following Enevoldsen's criteria, 57% of our series had an impaired/abolished autoregulation. The patient with a 22% reduction of estimated CBF was included in the 'intact' autoregulation group. Here, the reduction in CBF could be due to some hyperreactive vasoconstriction phenomenon with intact autoregulatory mechanisms. An increase in brain tissue pressure and a secondary reduction of CBF in a non-autoregulating patient (false autoregulation) [22] although possible, is less probable if we consider that in this case an increase of only 8 mm Hg of ICP was observed. Our data agree with other studies in that autoregulation is a very vulnerable mechanism and that impaired autoregulation is very common in head injury [18, 21, 53]. As Muizelaar has pointed out, autoregulation is not an all-or-none phenomenon and can be intact, slower than normal, intact with shifts in the pressure limits or show smaller adjustments than normal [50]. The 20% level in our study grossly distinguishes between intact and altered autoregulation. However, in the intact group, it is difficult to differentiate between patients with really normal autoregulation and those in whom lower or higher limits are abnormally shifted. When non-significant changes in $1/AVDO_2$ are produced after inducing increases in MABP, it can be assumed that autoregulation is intact, although shifts in its upper or lower thresholds are possible [64]. Impairment of autoregulation has also been demonstrated in ischaemic lesions and brain tumours in both the diseased and non-diseased hemispheres [55]. When testing autoregulation, it is important to consider the basal arterial pCO_2. It is well known that at high pCO_2, CBF is also high and therefore the resistance vessels are dilated and do not have enough dilatory capacity to keep CBF constant [18, 21]. Hypercapnia, dihydralazine, sodium nitroprusside, calcium antagonists and other drugs that act on the cerebrovascular bed could impair autoregulation [18, 21]. Speculating about theoretically responsible factors of impaired autoregulation in head injury can take into account the complex and multifactorial effects of brain injury and the treatment of these patients.

Impaired autoregulation and preserved CO_2-reactivity were found in 43% of the cases while preserved autoregulation and impaired CO_2-reactivity was not observed in any patient. Of the 28 cases in whom both autoregulation and CO_2-reactivity were studied, only five had a 'complete vasoparalysis' (impaired autoregulation and CO_2-reactivity). Our data are in complete agreement in that this total 'vasoparalysis' is infrequent and found only in the very severely damaged brain [55]. An interesting finding in our study was the observation that in spite of impaired autoregulation, increasing MABP induced a net increase of CPP in all but one patient. This finding supports that

to increase CPP by increasing MABP is not deleterious in patients with impaired autoregulation. However, no firm conclusions can be drawn about the effects of increasing capillary pressure and so facilitating its effect on brain oedema in non-autoregulating patients. Increasing mean blood pressure with vasoactive drugs has recently been introduced as an alternative treatment of high ICP in autoregulating patients [7, 49]. Nevertheless, optimal blood pressure management in severe head injured patients is still controversial [49]. While some authors advocate increasing CPP in the acute phase, this management could be theoretically hazardous in patients with disturbed autoregulation. Increasing CPP in this subgroup would increase CBV and capillary pressure, therefore encouraging brain oedema. According to Obrist *et al.*, about half the patients with a severe head injury have a variable degree of autoregulation impairment [53].

We can conclude that monitoring relative changes in $AVDO_2$ permits the reliable study of CO_2-reactivity and autoregulation at the bedside. This can increase our knowledge of these parameters and their changes in the evolution of the head injury patient. Introducing these variables on a day-to-day management basis should be considered in the treatment protocols. Knowledge of the CO_2-reactivity and autoregulation status in the acute phase of head injury is necessary to establish individualized treatment protocols and to avoid dangerous therapeutic manoeuvres in such a heterogeneous group of patients. A consensus of the range of normality for CO_2-reactivity and autoregulation would be desirable to standardize methods and to compare patients from different series.

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Comments

This is a very nice study on the alterations in the physiopathology of the cerebral circulation (autoregulation and vasoreactivity on CO_2) after head injury. The aim of the study is to give guidelines for a better therapeutic policy.

Only patients with diffuse lesions have been included in the study which supposes that they have diffuse alterations of the cerebral circulation measurable by analysis of jugular blood samples (global cerebral haemometabolism).

Question to the authors: why have you used $AVDO_2$ (= 1.34 Hb (SaO_2–SjO_2) instead of SjO_2? It is clear that variations of Hb can influence the significance of $AVDO_2$. In this study the Hb varies significantly between some patients (9.4–14.7 $g.dl^{-1}$) (see publications of Cruz *et al.*).

F. Cohadon

Answer of the Authors

The main reason for using $AVDO_2$ instead of SjO_2 to test CO_2-reactivity and autoregulation is that using SjO_2 assumes that Hb and SaO_2 do not change during the test. Although we can assume that Hb is constant, SaO_2 can move during the test due to better perfusion of the lungs or other reasons when changing pCO_2 or increasing mean arterial blood pressure. Although it is true that Cruz *et al.* have observed that $AVDO_2$ can be misleading when anaemia is present, this only involves comparisons between different patients or when trying to classify patients into different diagnostic groups (ischaemia, hyperaemia ...). The presence of anaemia is not a problem when relative changes in $AVDO_2$ are measured in the same patient at two different points in time. The variations in Hb in our study, were between different patients and not in the same patient during tests. Furthermore, in our opinion, Cruz's findings should be validated. Sensitivity and specificity of different haemometabolic variables have not yet been defined. A recent study by our Group (Sahuquillo, J., Poca, M. A., Garnacho, A., Báguena, M., Campos, L., Pellegri, M. D., and Rubio, E. *Is there aggreement between different methods we use in monitoring brain ischaemia?* A comparative study using arterio-jugular difference of oxygen ($AVDO_2$), oxyhaemoglobin saturation (SjO_2) and cerebral extraction of oxygen. In: Nagai H, Kamiya K, Ishii S (eds) (1994) Intracranial pressure IX. Springer, Berlin Heidelberg New York Tokyo pp. 42–45), showed that there is indeed little agreement between different methods used. For these reasons, we used the traditional approach in physiology of measuring total oxygen content, validated in other organs such as heart or lung to estimate CBF. We hope these reasons are satisfactory for the reviewers.

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