CEREBRAL VASCULAR AUTOREGULATION ASSESSED BY PERFUSION-CT IN SEVERE HEAD TRAUMA PATIENTS

M. WINTERMARK (1), R. CHIOLOERO (3), G. VAN MELLE (5), J.P. REVELLY (3), F. PORCHET (4), L. REGLI (4), P. MAEDER (2), R. MEULI (2), P. SCHNYDER (2)

(1) Department of Radiology, Neuroradiology Section, University of California, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143-0628, USA.
(2) Department of Diagnostic and Interventional Radiology,
(3) Surgical Intensive Care Unit,
(4) Department of Neurosurgery, University Hospital (CHUV), Lausanne, Switzerland.
(5) Biostatistics Unit, University Institute of Social and Preventive Medicine, Lausanne, Switzerland.

SUMMARY

Purpose: To use perfusion-CT technique in order to characterize cerebral vascular autoregulation in a population of severe head trauma patients with features of cerebral edema either on the admission or on the follow-up conventional noncontrast cerebral CT.

Material and methods: A total of 80 perfusion-CT examinations were obtained in 42 severe head trauma patients with features of cerebral edema on conventional noncontrast cerebral CT, either on admission or during follow-up. Perfusion-CT results, i.e. the regional cerebral blood volume (rCBV) and flow (rCBF), were correlated with the mean arterial pressure (MAP) measured during each perfusion-CT examination. Ratios were defined to integrate the concept of cerebral vascular autoregulation, and cluster analysis performed, which allowed identification of different subgroups of patients. MAP values and perfusion-CT results in these groups were compared using Kruskal-Wallis and Wilcoxon (Mann-Whitney) tests. Moreover, the functional outcome of the 42 patients was evaluated 3 months after trauma on the basis of the Glasgow Outcome Scale (GOS) score and similarly compared between groups.

Results: Three main groups of patients were identified: 1) 22 perfusion-CT examinations were collected in 13 patients, characterized by high rCBV and rCBF values and by significant dependence of perfusion-CT rCBV and rCBF results on MAP values (p<0.001), 2) 23 perfusion-CT examinations collected in 19 patients showing perfusion-CT results similar to control trauma subjects, and 3) 33 perfusion-CT collected in 16 patients, with low rCBV and rCBF values and near-independence of perfusion-CT results with respect to MAP values. The first group was interpreted as showing impaired cerebral vascular autoregulation, which was preserved in the third group. The second group was associated with the best functional outcome; it was linked to the first group, because eight patients went from one group to the other from admission to follow-up.

Conclusion: Perfusion-CT in severe head trauma patients was able to provide direct and quantitative assessment of cerebral vascular autoregulation with a single measurement. It could hence be used as a guide for brain edema therapy, as well as to monitor the treatment efficiency.

Key words: Brain edema, brain perfusion, head injuries, perfusion-CT.

RÉSUMÉ

Autorégulation vasculaire cérébrale évaluée par scanner de perfusion chez des patients victimes de traumatismes crâniens sévères

But : Caractériser l'autorégulation vasculaire cérébrale dans une population de patients traumatisés crânio-cérébraux sévères et avec signes d'oedème cérébral, sur le CT sans contraste obtenu soit à l'admission, soit durant le suivi.

Matériel et méthodes : Un total de 80 examens de CT de perfusion furent collectés chez 42 patients. Le résultat du scanner de perfusion, à savoir le volume sanguin cérébral régional (rCBV) et le flux sanguin cérébral régional (rCBF), furent corréls avec la pression artérielle moyenne (MAP) mesurée durant chaque CT de perfusion. Des rapports furent définis pour intégrer le concept d’autorégulation vasculaire cérébrale. Une analyse par groupe fut réalisée, qui permet d’identifier différents sous-groupes de patients. Les valeurs de MAP et les résultats de CT de perfusion dans les différents groupes furent comparés par des tests de Kruskall-Wallis et de Wilcoxon (Mann-Whitney). Par ailleurs, le devenir des 42 patients fut évalué 3 mois après le trauma sur la base de l’échelle fonctionnelle de Glasgow (GOS) et comparé d’un groupe à l’autre.

Résultats : Trois principaux groupes de patients furent identifiés : 1) 22 CT de perfusion furent collectés chez 13 patients, caractérisés par des valeurs élevées de rCBV et rCBF, et par une dépendance significative des valeurs de rCBV et rCBF comparées aux valeurs de MAP (p<0,001), 2) 23 CT de perfusion collectés chez 19 patients démontrèrent des valeurs de perfusion similaires à celles enregistrées chez les sujets contrôles. 3) 33 CT de perfusion furent collectés chez 16 patients, avec des valeurs basses de rCBV et rCBF, et une indépendance des valeurs de perfusion comparées aux valeurs de MAP. Le premier groupe fut interprété comme montrant une autorégulation vasculaire cérébrale altérée, alors que celle-ci était préservée dans

1The work was performed in the University Hospital (CHUV), Lausanne, Switzerland.

Reprint request: M. WINTERMARK, address above.
e-mail: max.wintermark@radiology.ucsf.edu
le troisième groupe. Le deuxième groupe avait le meilleur pronostic; il était lié au premier groupe, parce que huit patients migrèrent d’un groupe à l’autre depuis l’admission jusqu’au suivi.

**Conclusion:** Le scanner de perfusion utilisé chez les patients victimes de traumatismes cranio-cérébraux sévères est capable d’évaluer directement et quantitativement l’autorégulation vasculaire cérébrale et ce par une seule mesure. Cette technique pourrait de ce fait être utile pour orienter le traitement de l’œdème cérébral et poursuivre l’efficacité du traitement.

Mots-clés : Oedème cérébral, perfusion cérébrale, traumatisme crânien et scanner de perfusion.

**INTRODUCTION**

Two hypothetical mechanisms have been proposed to explain the development of cerebral edema in the setting of brain trauma [1]. The first hypothesis, accounting for the so-called “vasogenic edema”, relates to a loss of cerebral vascular autoregulation with subsequent brain hyperemia and to an impairment of the blood-brain barrier [1-6]. The second mechanism, referred to as “cytotoxic edema”, relates to an energetic ion pump failure of the cerebral parenchyma, leading to swollen brain cells and cell damage, with subsequent cerebral oedema [1, 5, 7, 8]. Cytotoxic edema is associated with either preserved cerebral vascular autoregulation or pseudautoregulation [9].

Characterization of the type of edema, and distinguishing between preserved (or pseudo) and altered cerebral vascular autoregulation, is clearly an important issue since it can affect treatment and outcome [10]. Treatment of vasogenic edema, associated with altered autoregulation, involves rather a controlled arterial normotension or even hypotension, according to the Lund’s concept [11-13]. Conversely, treatment of cytotoxic edema involves controlled arterial hypertension in order to ensure sufficient cerebral perfusion pressure, in addition to the treatment of intracranial hypertension [8, 14-19].

There is no simple technique allowing distinguishing between preserved and altered cerebral vascular autoregulation in individual brain-injured patients. Consequently, the selection of the therapeutic strategy is mostly empirical, rather than based upon defined targets and individually oriented. This issue is even more of concern since the effect of the different therapeutic strategies is influenced by the status of cerebral vascular autoregulation [15, 16, 20]. They may lead to iatrogenic complications, such as brain ischemia in case of hyperventilation, or worsening of brain edema and intracranial hypertension by arterial hypertension [21-24]. Considerable interest would be raised by a simple and noninvasive technique that would be sensitive to cerebral vascular autoregulation and would allow the introduction of treatment modalities tailored to every single patient.

Recently, perfusion-CT has been demonstrated as affording a direct insight into cerebral vascular autoregulation in the ischemic brain [26, 27]. It has consequently gained recognition in the early management of adult patients with acute stroke and of other cerebrovascular disorders [26-28]. Perfusion-CT has also been reported as a clinical outcome predictor in severe head trauma patients [29]. It only involves dynamic acquisition of sequential CT slices on a cine mode during intravenous administration of non-ionic iodinated contrast material. Perfusion-CT does not interfere with the contrast-enhanced chest-abdomen-pelvis CT survey performed in severe trauma patients, and with the detection of traumatic visceral injuries, such as traumatic splenic lesions [29].

Because cerebral vascular autoregulation is altered similarly in stroke and in brain trauma [30], we decided to evaluate in this study whether perfusion-CT technique was adequate to characterize cerebral vascular autoregulation in a population of severe head trauma patients with features of cerebral edema either on the admission or on the follow-up conventional noncontrast cerebral CT.

**MATERIALS AND METHODS**

**Patients**

During the period from July 2001 to October 2002, all intubated adult trauma patients with a Glasgow Coma Scale (GCS) score on admission of 8 or less were prospectively identified in the Emergency Room of our hospital. In our institution, such patients undergo routine noncontrast cerebral, non-contrast cervical and contrast-enhanced chest-abdomen-pelvis multidetector-row CT. As part of a general study [29], a perfusion-CT examination was additionally obtained on admission. Perfusion-CT series were also performed during follow-up contrast-enhanced cerebral CT. The study protocol was approved by the ethical committee for research of the Lausanne University.

Two subgroups of the patients enrolled in the general study were considered separately. Inclusion criteria for both subgroups are explained in figure 1. The first group (42 patients) was selected to evaluate whether perfusion-CT technique is adequate to characterize cerebral vascular autoregulation in severe head trauma patients. The patients from the second group (32 patients) were considered as the control trauma subjects of the study.

**Imaging protocol**

A perfusion-CT series was performed immediately after the noncontrast cerebral CT and before the cervical CT and the CT-angiogram of the thoracic and lumbar aorta. It consisted of a 40-second series, with 40 gantry rotations performed at a rate of 1 rotation per second in cine mode during intravenous administration of iodinated contrast material. The CT scanner used was a 16-slice scanner. The acquisition parameters for the perfusion-CT were 80kVp and 100mAm. Perfusion-CT scanning was initiated 7 seconds after injection of 40mL of iohexol.
(300mg/mL of iodine; Accupaque 300, Nycomed, Oslo, Norway) at a rate of 5mL per second into an antecubital vein using a power injector (CT9000; Libel-Flarsheim Company, Cincinnati, Ohio). Multidetector-row CT technology afforded the assessment of two adjacent 10-mm-thick slices. The two studied cerebral slices were selected above the orbits to protect the lenses, at the level of the third ventricle and the basal nuclei, then towards the vertex.

**Data processing**

The perfusion-CT data were analyzed using perfusion-CT software developed by Philips Medical Systems World Headquarters (Best, Netherlands). This software relies on the central volume principle, the most accurate for low injection rates of iodinated contrast material [31], based on a mathematical operation called deconvolution [32-34]. The software leads to the calculation of three brain perfusion parametric maps: regional cerebral blood flow (rCBF) and volume (rCBV), and mean transit time (MTT) (35-37).

**Clinical data**

Patient management involved controlled mechanical ventilation, continuous intracranial pressure (ICP) monitoring, osmotherapy (mannitol 20%) and controlled sedation and analgesia (propofol and fentanyl, or remifentanyl) in case of intracranial hypertension. Intracranial hypertension was diagnosed either when invasive measurement of ICP was superior to 18mmHg, or when CT patterns of herniation were present in patients without ICP monitoring.

Mean radial or femoral arterial pressure values were recorded for each patient during the admission and follow-up cerebral CT examinations. The mean arterial pressure (MAP) measurements considered for comparison with perfusion-CT results were typically those averaged over the 5-10 minutes while the patient lay on the CT table.

As part of the general study, the functional outcome was evaluated 3 months after trauma during neurosurgical follow-up, or by the family doctor on the basis of the Glasgow Outcome Scale (GOS) score (5 – good recovery: good outcome with minimal to no dysfunction; 4 – moderate disability: minimal functional abnormality and no interference with daily life activities; 3 – severe disability requiring institutional care; 2 – vegetative state: no reaction to outside stimuli; 1 death: 1a primary lesion, 1b late complication).

**Data analysis**

For each perfusion-CT examination and for each of the maps extracted from perfusion-CT data, describing rCBV, MTT and rCBF values, respectively, one single average value was obtained for the gray matter displayed on the two perfusion-CT slices. Gray matter was automatically segmented on the contrast-enhanced CT images using Hounsfield unit thresholds. Pixels containing large vessels were automatically discarded from the measurements by the post-processing software, based on a CBV threshold.

**Statistical analysis**

The statistical analysis was performed using the commercial software Stata 8.0 (StataCorp LP, College Station, Texas) and included two steps.
The first step focused on the concept of cerebral vascular autoregulation. The rCBV and rCBF parameters were inspected with respect to the MAP value measured during the corresponding perfusion-CT examination. Data appeared to cluster along two lines. Guided by the results of a previous study showing a dual distribution of perfusion-CT results in head trauma patients [38], we performed a cluster analysis of the rCBF/MAP data. Three groups emerged: low rCBF/low MAP, low rCBF/high MAP and high rCBF/high MAP. The low rCBF/low MAP group represented the “intersection” of the two lines. All possible allocations of the points in this low rCBF/low MAP cluster to either line were tried out. For each allocation, a linear regression was computed in each group. The allocation with the highest overall R² (weighted) was considered the best one. The second part of the statistical analysis used the rCBV/MAP (volume-to-pressure) and rCBF/MAP (flow-to-pressure) ratios to categorize the perfusion-CT examinations obtained in this study. The examinations clustered into three well-separated groups, with three outliers. Examinations showing high volume- and flow-to-pressure ratios were labeled Group 1 (high ratios), examinations showing intermediate values of volume- and flow-to-pressure ratios were labeled Group 2 (normal ratios), and examinations showing low volume- and flow-to-pressure ratios were labeled Group 3 (low ratios). MAP values, perfusion-CT results and derived ratios were compared between the examinations obtained in the control trauma subjects and the three above-mentioned groups using Kruskal-Wallis tests. When this Kruskal-Wallis test was significant, the statistical significance was checked by comparing each “pathological” group with examinations obtained in the control trauma subjects with a Wilcoxon (Mann-Whitney) test. For both the Kruskal-Wallis and the Wilcoxon tests, the significance level set at 0.001 to account for the multiple testing (Bonferroni).

RESULTS

Patients

Forty-two patients were enrolled in the present study according to the algorithm reported in figure 1. Our series consisted of 32 male and 10 female patients, with a median age of 32 and an interquartile range of 27.5 to 49 (range of 19 to 76). Twenty-nine patients were injured in traffic accidents (76%=22/29 in car accidents, 17%=5/29 in motorcycle accidents, 7%=2/29 as pedestrians), 11 in falls and 2 in crush accidents.

Each patient underwent perfusion-CT on admission. Beside these 42 admission examinations, a total of 38 follow-up perfusion-CT examinations were obtained in the days following admission (median=1.5 days, range=16 hours to 5 days). The number of follow-ups per patient ranged from 0 to 3. Thus, a total of 80 perfusion-CT examinations were collected in the present study. All perfusion-CT examinations were well tolerated, with no reported side effects.

Among the 137 patients, 32 patients were identified as control trauma subjects according to the algorithm reported in figure 1. Five of these subjects had a follow-up perfusion-CT. Hence, the control group consisted of a total of 37 control perfusion-CT examinations.

Noncontrast cerebral CT findings

The noncontrast cerebral CT findings are reported in table I.

Perfusion-CT results

The average values calculated in the control trauma subjects and in the 80 perfusion-CT examinations collected in patients with CT features of cerebral edema are reported in table II.

Association between perfusion-CT results and MAP values

In the control trauma subjects without cerebral edema (red circles on figure 2), the rCBV and rCBF values were unrelated to the corresponding MAP values.

Patients with CT features of cerebral edema (blue squares on figure 2) appeared distributed in around two straight lines.

The first line (double line) was characterized by a wide range of rCBV (43.9±0.9 ccx100g⁻¹) and rCBF values (19.6±22.3 ccx100g⁻¹xmin⁻¹), and by a strong dependence of these rCBV and rCBF values on the corresponding MAP values. The typical perfusion-CT results observed in a patient belonging to the first line are shown in figure 3. The strong dependence of rCBV and rCBF values on the corresponding MAP values is. The steep slope corresponds to high rCBV/MAP (volume-to-pressure) and rCBF/MAP (flow-to-pressure) ratios.

The second line (single line) was characterized by significantly lower rCBV (1.8±0.4 ccx100g⁻¹ (mean±SD)) and rCBF values (19.6±7.1 ccx100g⁻¹xmin⁻¹) than in the control trauma subjects (p<0.001), and by a weak dependence of these rCBV and rCBF values on the corresponding MAP values. The typical perfusion-CT results observed in a patient belonging to the second line are shown in figure 4a. The low slope corresponds to low rCBV/MAP (volume-to-pressure) and rCBF/MAP (flow-to-pressure) ratios.

Derived perfusion-CT results: combination of rCBV/MAP and rCBF/MAP ratios

The relationship between rCBF/MAP and rCBV/MAP ratios is represented on figure 4a, both for control trauma subjects (red square=mean±2 standard deviations of values in the control group) and for patients with CT features of cerebral edema (blue squares).

Cluster analysis afforded to categorize patients with CT features of cerebral edema into three groups, shown as three black circles on figure 4b, with three outliers.

The MAP values, perfusion-CT results and rCBV/MAP and rCBF/MAP ratios in the control trauma...
subjects and in the three groups of patients with CT features of cerebral edema are reported in table II.

Group 1 (high ratios, black circle #1 on figure 4b) included 21 perfusion-CT examinations collected in 12 patients. Mean MAP value in Group 1 was not significantly different from the one measured in control trauma subjects. On the other hand, rCBV and rCBF values were significantly higher. rCBV/MAP and rCBF/MAP ratios were also significantly higher than in the control trauma subjects (p<0.001). These high rCBV/MAP and rCBF/MAP ratios were related:
— either to very high rCBV and rCBF values together with moderate to high MAP values (blue squares clustering around the right superior portion of the steep straight line on figure 2);
— or to low rCBV and rCBF values together with even lower MAP values (blue squares clustering around the left inferior portion of line of the steep straight line on figure 2).

Group 2 (normal ratios, black circle #2 on figure 4b) included 23 perfusion-CT examinations collected in 19 patients. MAP values, rCBV and rCBF results and rCBV/MAP and rCBF/MAP ratios in Group 2 were similar to the values observed in control trauma subjects. These results corresponded to the blue squares clustering around the intermediate portion of the steep straight line on figure 2.

Group 3 (low ratios, black circle #3 on figure 4b) included 33 observations collected in 16 patients. MAP values in Group 3 were not significantly different from the values in the control trauma subjects. Patients from Group 3 were characterized by rCBV/MAP and rCBF/MAP ratios that were significantly lower (p<0.001) than in control trauma subjects. These low rCBV/MAP and rCBF/MAP ratios related to significantly lower rCBV and lower rCBF values associated with preserved MAP values. Patients from Group 3 were those clustering around the low-slope straight line on figure 2.

The patient labeled as Outlier #1 on figure 4b was considered as an extreme representative of patients belonging to group #1. This patient showed the highest rCBV/MAP and rCBF/MAP ratios, corresponding to high rCBV and rCBF values for a moderately increased MAP value, as displayed on figure 2. This patient died from intracranial hypertension two days after admission.
TABLE II. – Mean and standard deviation (mean±SD) of MAP values, perfusion-CT results, rCBV/MAP and rCBF/MAP ratios in the control trauma subjects without cerebral edema, in the three groups of patients with CT features of cerebral edema and in Outliers #2 and #3. The Kruskal-Wallis test was used to compare these parameters among the four groups and, when this Kruskal-Wallis test was significant (p<0.001), the statistical significance was checked by comparing each “pathological” group with the control group with a Wilcoxon (Mann-Whitney) test (p value shown in parentheses).

<table>
<thead>
<tr>
<th>Number of perfusion-CT examinations</th>
<th>Control trauma subjects without cerebral edema</th>
<th>All patients with cerebral edema (Groups #1 +#2 +#3)</th>
<th>First Group (high rCBV and rCBF values)</th>
<th>Second Group (intermediate rCBV and rCBF values)</th>
<th>Third Group (low rCBV and rCBF values)</th>
<th>Outliers #2 and #3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37</td>
<td>80</td>
<td>21+outlier #1=22</td>
<td>23</td>
<td>33</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean Arterial Pressure (MAP) [mmHg] *

<table>
<thead>
<tr>
<th>rCBV [c.c.×100g⁻¹]</th>
<th>3.2±0.6 (p=0.166)</th>
<th>3.1±1.1 (p=0.001)</th>
<th>4.2±0.6 (p&lt;0.001)</th>
<th>3.2±0.4 (p&lt;0.001)</th>
<th>1.9±0.4 (p&lt;0.001)</th>
<th>4.8±0.9 (p&lt;0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF [c.c.×100g⁻³x.min⁻¹]</td>
<td>48.8±10.1 (p=0.092)</td>
<td>43.9±27.2 (p&lt;0.001)</td>
<td>77.9±11.5 (p=0.185)</td>
<td>46.0±9.5 (p&lt;0.001)</td>
<td>19.6±7.1 (p&lt;0.001)</td>
<td>27.0±3.7 (p&lt;0.001)</td>
</tr>
<tr>
<td>MTT [sec]</td>
<td>4.3±0.8 (p=0.107)</td>
<td>5.1±2.8 (p=0.001)</td>
<td>3.5±0.3 (p=0.139)</td>
<td>4.6±0.5 (p&lt;0.001)</td>
<td>7.3±2.4 (p&lt;0.001)</td>
<td>10.8±2.2 (p&lt;0.001)</td>
</tr>
<tr>
<td>rCBV/MAP</td>
<td>0.036±0.008 (p=0.251)</td>
<td>0.033±0.006 (p=0.001)</td>
<td>0.044±0.007 (p=0.001)</td>
<td>0.038±0.004 (p=0.001)</td>
<td>0.021±0.003 (p=0.001)</td>
<td>0.049±0.012 (p=0.007)</td>
</tr>
<tr>
<td>rCBF/MAP</td>
<td>0.527±0.124 (p=0.212)</td>
<td>0.479±0.098 (p=0.001)</td>
<td>0.814±0.097 (p=0.370)</td>
<td>0.549±0.069 (p=0.001)</td>
<td>0.219±0.076 (p=0.001)</td>
<td>0.280±0.134 (p=0.003)</td>
</tr>
</tbody>
</table>

* for mean arterial pressure (MAP), no difference between the different categories of patients (p=0.462) according to the Kruskal-Wallis test; for all the other parameters, there was a statistically significant difference (p<0.001).

Fig. 2. – Perfusion-CT values of rCBV and rCBF expressed in terms of the corresponding MAP values, both for control trauma subjects (red circles) and for patients with CT features of cerebral edema (blue squares). In the control trauma subjects, rCBV and rCBF are essentially independent of the corresponding MAP values, whereas patients with CT features of cerebral edema appear to cluster around two lines. One line (single line) is characterized by significantly lower rCBV and rCBF values than in the control group, and by a weak dependence of these rCBV and rCBF values on the corresponding MAP values (low slope). The second line (double line) is characterized by a wide range of rCBV and rCBF values, and by a strong dependence of these rCBV and rCBF values on the corresponding MAP values (steep slope).

Fig. 2. – Valeurs de volume (rCBV) et flux (rCBF) sanguins cérébraux régionaux obtenues par CT de perfusion et exprimées en fonction des valeurs correspondantes de pression artérielle moyenne (MAP), à la fois chez les sujets contrôles (cercles rouges) et chez les patients avec des signes d’œdème cérébral (carrés bleus). Chez les sujets contrôles, les valeurs de rCBV et de rCBF sont indépendantes des valeurs correspondantes de MAP, alors que les patients avec des signes d’œdème cérébral se regroupent le long de deux droites. Une des droites (ligne simple) est caractérisée par des valeurs de rCBV et de rCBF significativement plus basses que dans le groupe contrôle, et par une faible dépendance des valeurs de rCBV et de rCBF comparées aux valeurs de MAP (faible pente). La deuxième droite (ligne double) est caractérisée par une large gamme de valeurs de rCBV et rCBF, et par une forte dépendance de ces valeurs comparées aux valeurs correspondantes de MAP (pente raide).
Fig. 3. – Patient involved as a passenger in a high-speed car accident. Conventional contrast-enhanced cerebral CT demonstrates diffuse edema with swollen brain parenchyma and absent basal cisterns. Perfusion-CT series demonstrate high rCBF and rCBV in both sylvian territories (stars). Mean arterial pressure (MAP) averaged over the 5-10 minutes while the patient lay on the CT table, was 102 mmHg. The rCBF/MAP and rCBV/MAP ratios calculated for both sylvian territories were high (0.899 and 0.063, respectively). Interestingly, oligemia (low rCBF and rCBV) and low rCBF/MAP and rCBV/MAP ratios (0.019 and 0.285, respectively) were observed in left frontal pole and in both occipital areas. This observation suggests that different patterns of altered autoregulation can coexist in the same severe head trauma patient, even if one pattern predominates.

Fig. 4. – a) Relationship between the flow-to-pressure ratio rCBF/MAP and the volume-to-pressure ratio rCBV/MAP, both in control trauma subjects (red square = mean ± 2 standard deviations of values in the control group) and in the patients with CT features of cerebral edema (blue squares). b) Cluster analysis afforded to categorize patients with CT features of cerebral edema into three groups, shown as three black circles, and three outliers. c) Our proposed interpretation for the observed patterns of brain perfusion is a loss of cerebral vascular autoregulation in group #1 (with outlier #1 representing an extreme case of group #1) and a preserved or pseudo-autoregulation in group #3. The types of brain edema developing in this setting are classically referred to as “vasogenic edema” and “cytotoxic edema”, respectively. Patients from group #2 would show less severely impaired autoregulation, or better answer to treatment. Finally, outliers #2 and #3 feature relatively high rCBV values and relatively low rCBF values. They were characterized clinically by elevated central venous pressure, consecutive to high PEEP values in one case and to central venous thrombosis in the other. The brain edema observed in these two patients might correspond to a pattern of “venous congestion” edema.
The two observations collected from the two patients labeled as Outliers #2 and #3 (figure 4b) were considered separately. These patients were characterized by a trend leaning towards higher rCBV values and rCBV/MAP ratios, and lower rCBF values and rCBF/MAP ratios. MAP values were not significantly different from the control group. Clinically, one of these two patients showed adult respiratory distress syndrome, with extensive consolidations on the chest CT, and required high positive-expiratory end-pressure (PEEP) during mechanical ventilation at the time of the perfusion-CT examination. The other patient demonstrated thrombosis of his venous jugular catheter, this thrombosis extending down into the innominate vein and the superior vena cava.

Perfusion-CT results from admission and follow-up examinations: evolution with time

Eight patients showed overlapping evolution from group #1 to group #2, or from group #2 to group #1, from admission to follow-up. On the contrast, all patients in group #3 who underwent follow-up perfusion-CT examinations remained in group #3.

The 24 patients of the black circles #1 and #2 (including outlier #1) underwent a perfusion-CT examination on admission, as well as a total of 21 follow-up perfusion-CT. These follow-up examinations were obtained after a median delay of 2 days (range=18 hours to 5 days).

The 16 patients of the black circle #3 underwent a perfusion-CT examination on admission, as well as a total of 17 follow-up perfusion-CT. These follow-up examinations tended to be obtained after a shorter delay (median=1.5 days, range=16 hours to 4 days), but the difference was not significative (p=0.176).

Intracranial hypertension

For the different groups and subgroups, the number of patients diagnosed with intracranial hypertension during their hospitalization is reported in table III.

Functional Outcomes

Functional outcomes measured on the basis of the GOS score at three months in the different groups and subgroups of patients are displayed in table III.

DISCUSSION

We reported about a series of 80 perfusion-CT examinations, which were collected in 42 severe head trauma patients with CT features of cerebral edema, either on admission or during follow-up. These observations were derived from a subgroup of a larger study [29], which was the first study assessing the use of perfusion-CT in head trauma patients. The goal of the present substudy was to evaluate

| TABLE III. – Prevalence of intracranial hypertension and functional outcome in different groups of patients identified within patients with CT features of cerebral edema, including the p values of the comparisons of respective functional outcomes using Kruskal-Wallis or Wilcoxon (Mann-Whitney) rank-sum tests. | | Number of patients | Number of patients with intracranial hypertension | Glasgow Outcome Scale (GOS) Score at 3 months | p value |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| patients with only 1 perfusion-CT examination | group 1+outlier 1 on Fig 4b | 4 | 4 | 2.5±1.2 | p<0.001 (Kruskal-Wallis) |
| | group 2 on Fig 4b | 7 | 0 | 3.8±1.1 |
| | group 3 on Fig 4b | 5 | 5 | 2.1±0.8 |
| patients with follow-up perfusion-CT examinations | remaining in group 3 on Fig 4b | 11 | 11 | 1.8±1.0 |
| | remaining in group 1 on Fig 4b | 1 | 1 | 2.2±1.2 | p<0.001 (Wilcoxon) |
| | going from group 2 to group 1 on Fig 4b | 5 | 5 | 3.6±0.9 |
| | remaining in group 2 on Fig 4b | 4 | 1 | 3.6±0.9 |
| | going from group 1 to black circle 2 on Fig 4b | 3 | 2 | 3.6±0.9 |

The 24 patients of the black circles #1 and #2 (including outlier #1) underwent a perfusion-CT examination on admission, as well as a total of 21 follow-up perfusion-CT. These follow-up examinations were obtained after a median delay of 2 days (range=18 hours to 5 days).

The 16 patients of the black circle #3 underwent a perfusion-CT examination on admission, as well as a total of 17 follow-up perfusion-CT. These follow-up examinations tended to be obtained after a shorter delay (median=1.5 days, range=16 hours to 4 days), but the difference was not significative (p=0.176).

Intracranial hypertension

For the different groups and subgroups, the number of patients diagnosed with intracranial hypertension during their hospitalization is reported in table III.

Functional Outcomes

Functional outcomes measured on the basis of the GOS score at three months in the different groups and subgroups of patients are displayed in table III.

DISCUSSION

We reported about a series of 80 perfusion-CT examinations, which were collected in 42 severe head trauma patients with CT features of cerebral edema, either on admission or during follow-up. These observations were derived from a subgroup of a larger study [29], which was the first study assessing the use of perfusion-CT in head trauma patients. The goal of the present substudy was to evaluate
cerebral vascular autoregulation in head trauma patients using perfusion-CT technique.

In our series of head trauma patients with brain edema, perfusion-CT quantitative results combined with MAP values afforded to distinguish between three patterns among the patients with CT features of cerebral edema, as displayed in figure 4c.

The first pattern of perfusion-CT examinations, encountered in 24 (57%) patients (groups #1, high ratios, and #2, normal ratios), is mainly characterized by a dependence of perfusion-CT results upon MAP values, featuring significantly higher volume-to-pressure and flow-to-pressure ratios. Eight patients showed overlapping evolution from group #1 to group #2, or from group #2 to group #1, from admission to follow-up. Functional outcome was favorable in the groups #1 and #2, especially in patients going from group #1 to group #2. On the other hand, intracranial hypertension was more frequent in patients remaining in group #1 or going from group #2 to group #1. The brain perfusion pattern observed in groups #1 and #2 can be explained by a loss of cerebral vascular autoregulation, with high or low cerebral perfusion values depending on whether MAP values were high or low. The type of brain edema developing in case of loss of cerebral vascular autoregulation is classically referred to as "vasogenic edema".

The second pattern, encountered in 16 (38%) patients (group #3, low ratios), is characterized by significantly low volume-to-pressure and flow-to-pressure ratios. These ratios relate to low rCBV and rCBF values, i.e. to cerebral oligemia, and near-independence with respect to MAP values. Functional outcome was rather unfavorable in group #3. The brain perfusion pattern observed in group #3 suggests preservation of cerebral vascular autoregulation, or rather pseudo-autoregulation [9]. The type of brain edema developing in case of preserved or false cerebral vascular autoregulation is classically referred to as "cytotoxic edema", characterized by a reduced vascular compartment of the brain secondary to swollen cerebral parenchyma. The absence of overlap between group #3 and groups #1 and #2 suggests that one type of edema tends to predominate in severe head trauma patients. However, this remains to be confirmed in a larger study focusing on the time course of brain edema patterns in severe head trauma patients.

Finally, two patients showed a different pattern featuring relatively high rCBV values and relatively low rCBF values. These patients were characterized clinically by elevated central venous pressure, consecutive to high PEEP values in one case, and to central venous thrombosis in the other. The brain edema observed in this two patients might correspond to a pattern of "venous congestion" edema. The rCBF is determined by the MAP, the intracranial pressure, the blood viscosity and the diameter of arteries and arterioles, while the rCBV is mainly determined by the diameter of venules and arterioles, the latter being the only common denominator of rCBF and rCBV [40].

Cerebral vascular autoregulation encompasses a double concept: 1) the ability of the brain to adjust its regional perfusion to the local hemodynamic conditions; 2) the ability of the brain to maintain its global perfusion at a constant level independently of the systemic hemodynamic conditions. Perfusion-CT has been reported in the literature as an adequate tool to assess the first concept [26, 27]. Our goal in this study was to demonstrate that perfusion-CT can also address the second concept.

Classically, techniques to assess autoregulation involve a challenge, with induced modification of the blood pressure and repeated measurements of a specific parameter. The variations in the considered parameter are then correlated with the corresponding blood pressure variations, and information about autoregulation is inferred [41, 42]. Repeated measurements are required because the parameter studied in each challenge affords only an indirect evaluation of brain perfusion.

On the other hand, perfusion-CT technique affords direct quantitative assessment of brain perfusion, as demonstrated by comparison with stable xenon CT [43, 44] and PET [45]. Consequently, we hypothesized that, with a single measurement, perfusion-CT could be used to directly assess autoregulation by showing whether brain perfusion is constant at a normal level, or if it follows an abnormally elevated or low arterial blood pressure. Our results support this hypothesis.

We acknowledge several limitations to our study. The patients enrolled in the present study, particularly those with intracranial hypertension, underwent different kinds of treatment, responsible for the modifications of MAP and perfusion-CT values between the initial and the follow-up examinations. However, the present study was not designed to compare the effect of different therapeutic protocols on brain perfusion as featured by perfusion-CT, but to correlate MAP values with the perfusion-CT results. Both parameters were obtained simultaneously, which was the only requirement to achieve our goal, i.e. to evaluate whether perfusion-CT results was adequate or mismatched with respect to the MAP values.

We did not discuss relationship between perfusion-CT results, intracranial pressure and cerebral perfusion pressure, because this relationship has been reported before [38].

We decided to choose a subgroup of head trauma patients with no abnormal findings and with excellent functional outcome as our control trauma subjects, rather than a group of normal patients. Our controls have the same epidemiological characteristics and the same examination settings as the study patients. More specifically, they received the same analgesics and sedative drugs, which would not have been the case if the controls were normal non-traumatic patients. Our control trauma subjects were sedated and intubated because of pain, agitation on the accident site, or because of extracranial injuries,
such as limb fractures. The possible repercussions of sedation on brain perfusion must be mentioned, although dedicated imaging studies have suggested that the effect of sedation on cerebral blood flow was limited [46]. In any case, since both the study patients and the control trauma subjects underwent the same sedation, perfusion-CT differences between the two groups could not be explained solely by the sedation.

CONCLUSION

Our results support perfusion-CT as being a non-invasive tool affording direct and quantitative assessment of cerebral vascular autoregulation with a single measurement in severe head trauma patients. These results will have to be confirmed in larger studies, and perfusion-CT confronted to the classical diagnostic challenges used to assess cerebral vascular autoregulation. Future studies will also have to assess the ability of perfusion-CT to evaluate regional alterations of cerebral autoregulation in patients with a mixed pattern of cytotoxic and vasogenic edema, and monitor and guide brain edema treatment.

ACKNOWLEDGMENTS: The authors wish to acknowledge the competence of Mrs. L. de Palma as a research assistant in the Department of Diagnostic and Interventional Radiology.

REFERENCES

[29] EASTWOOD JD, LEV MH, PROVENZALE JM. Perfusion CT with iodinated contrast material. AJR 2003; 180: 3-12.


