ORIGINAL ARTICLE

Perfusion-CT assessment of the cerebrovascular reserve: A revisit to the acetazolamide challenges

Évaluation de la réserve cérébrovasculaire par scanner de perfusion: une revisite des tests à l’acétopazolamide

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KEYWORDS
Perfusion-CT; Acetazolamide challenge; Cerebrovascular reserve; Carotid stenosis

Summary
Background and purpose. — Imaging techniques utilizing acetazolamide challenges classically measure cerebral blood flow (CBF). In addition to measuring CBF, Perfusion-CT (PCT) can also assess cerebral blood volume (CBV) and mean transit time (MTT), expanding but also complicating the results of acetazolamide challenges performed using PCT. The goal of this study is to clarify the interpretation of PCT studies obtained during acetazolamide challenges.

Methods. — Four consecutive patients were referred for evaluation of their cerebrovascular reserve because of suspected or known large vessel stenosis or occlusion. In one patient, the potential stenosis was found to be artifactual, and this subject was considered as a normal control. The remaining three patients had clinical histories clearly suggestive of a worsening in cerebrovascular reserve (no.1 with a single transient ischemic attack (TIA), no.2 with several TIAs, no.3 with multiple, prolonged TIAs). All patients underwent a baseline PCT scan, followed by intravenous injection of 1 g acetazolamide and, 20 min postinjection, by a second PCT scan at exactly the same locations as the first. PCT cerebral blood flow, volume, and mean transit time values were measured in regions of interest (ROIs) encompassing the brain tissue at-risk and the normal brain tissue, defined based on the site of occlusion and the anatomy of the Circle of Willis. Changes in PCT parameters were calculated in corresponding ROIs on pre- and postacetazolamide PCT maps.

Results. — As compared to the normal control patient, baseline CBF values in the at-risk regions were similar in patients nos.1 and 2, and lower in patient no.3. After acetazolamide administration, CBF increased by 32% in the normal patient and decreased by 11, 11, and 9% in...
Introduction

Cerebrovascular reserve is a parameter frequently measured in patients with chronic cerebrovascular ischemic disease in order to determine the severity of disease and the associated risk of ischemic stroke, and to decide when bypass surgery should be performed [1,2].

Evaluation of the cerebrovascular reserve usually involves measurement of the cerebral blood flow (CBF) and its changes before and after an acetazolamide challenge [2]. A compromised cerebrovascular reserve is diagnosed when CBF decreases on the side of the vascular stenosis or occlusion after intravenous administration of acetazolamide, which normally results in an increase in CBF [1,2,3].

CBF measurements for acetazolamide challenges have been performed using positron emission tomography [4], single photon emission computed tomography [5], stable xenon-CT [6], magnetic resonance imaging (MRI) [7,8,9,10], Doppler ultrasound [11,12], and more recently, perfusion-CT (PCT) [13,14,15,6,16,17,18]. Some advantages of PCT include its widespread availability, ease of use, short exam duration, and quantitative results [13,15,2]. However, PCT assesses not only CBF, but also cerebral blood volume (CBV) and mean transit time (MTT), expanding and complicating the results of acetazolamide challenges performed using...
Perfusion-CT assessment of the cerebrovascular reserve: A revisit to the acetazolamide challenges

There are currently no standardized guidelines on how best to interpret the CBF, CBV and MTT results of PCT during acetazolamide challenges. The goal of this study is to clarify the interpretation of PCT studies and PCT parameters (CBF, CBV and MTT) obtained during acetazolamide challenges.

Materials and methods

Patients and imaging studies

Four consecutive patients were referred for evaluation of their cerebrovascular reserve because of symptoms suspicious for transient ischemic attacks (TIAs) and suspected or known large vessel stenosis or occlusion.

As part of the standard clinical care, these patients underwent a baseline PCT scan, followed by intravenous injection of 1 g acetazolamide and 20 min postinjection, by a second PCT scan at exactly the same locations as the first. The second PCT was followed by a CT-angiogram (CTA) of the cervical and intracranial arteries. The total volume of iodinated contrast injected to the patient was 210 ml.

Imaging data were retrospectively reviewed with the approval of the institutional review board.

Imaging protocols

PCT consisted of a 45 s series with 45 gantry rotations performed in cine mode during intravenous administration of iodinated contrast material. Images were acquired and reconstructed at a temporal sampling rate of 1 image/s, resulting in a series of 45 images for each assessed slice. The first PCT scan prior to the intravenous administration of acetazolamide included two successive PCT series that were separated by a time interval of 3—5 min and afforded a total coverage of 40 mm (4 × 10 mm). The two slices of the first PCT series were at the level of the third ventricle and the basal ganglia. The second PCT series was selected at a level 3.5 cm cranial to the first slice of the first series. For each PCT series, a 40 ml bolus of iohexol (Omnipaque, Amersham Health, Princeton, NJ; 300 mg/ml of iodine) was administered into an antecubital vein using a power injector at an injection rate of 5 ml per second for all patients. The acquisition parameters were 80 kVp and 100 mAs. CT scanning was initiated 7 s after start of the injection of the contrast bolus. The second PCT scan 20 min after intravenous administration of acetazolamide also included two successive PCT series, which were selected at exactly the same locations as the first.

The CTA was performed using the following parameters: 120 kVp, 240 mAs, slice thickness 1.25 mm, slice acquisition interval 1 mm, pitch 1.375:1, intravenous administration of 70 ml of iodinated contrast material at a rate of 4—5 ml per second, and an acquisition delay calculated from the PCT ranging from 14 to 29 s. Data acquisition was performed from the origin of the aortic arch branch vessels to the vertex.

Perfusion-CT postprocessing

PCT data were analyzed by a neuroradiologist utilizing PCT software developed by Philips Medical Systems (Cleveland, OH). This software relies on the central volume principle, which is the most accurate for low injection rates of iodinated contrast material [19]. After motion correction and noise reduction by an anisotropic, edge-preserving spatial filter, the software applies curve fitting by least mean squares to obtain mathematical descriptions of the time—density curves for each pixel. A closed-form (non-iterative) deconvolution operation is then applied to calculate the MTT map [20]. The deconvolution operation requires a reference arterial input function (most often within the anterior cerebral artery), selected by the PCT software within a region of interest drawn by the user. The CBV map is calculated from the area under the time—density curves [21]. CBF is calculated as CBV divided by MTT.

Image review and interpretation

CTAs were reviewed independently of PCT by a second neuroradiologist, who defined the brain tissue at-risk and the normal brain tissue based on the location of occlusive disease and the anatomy of the Circle of Willis.

A trained research assistant hand-drew up to fourteen regions of interest (ROIs) on each PCT slice (total of ROIs per patient = 44) corresponding to left and right basal ganglia and separate gray and white matter areas supplied by the left and right anterior cerebral arteries (ACA), middle cerebral arteries (MCA), and posterior cerebral arteries (PCA). Additional ROIs were drawn in the watershed areas between the vascular territories. This template set of standardized ROIs was adjusted to fit individual anatomy and applied to each patient. When hand-drawing the ROIs, the research assistant was blinded to clinical information and CTA interpretation. The research assistant processed the pre- and the postacetazolamide PCT datasets at the same time, but was blinded to which one was the preacetazolamide and postacetazolamide dataset. CBF, CBV and MTT values were recorded in all ROIs.

Once all template ROIs were fitted and all PCT values recorded, CTA interpretation was taken into account; each ROI (and corresponding PCT measurements) were attributed to either normal brain tissue or tissue at risk.

Changes in PCT parameters were calculated in corresponding ROIs on pre- and postacetazolamide PCT maps. Pre- and postacetazolamide values, as well as values within the at-risk brain tissue and the normal brain tissue, were compared using paired T-tests. Statistical significance threshold was set at 0.05.

Results

Normal control subject

An asymptomatic 55-year-old female was referred for evaluation of cerebrovascular reserve based on a left internal carotid artery stenosis seen on an MRI and magnetic resonance angiography (MRA) study at an outside hospital (Fig. 1). The stenosis was determined on the CTA following the acetazolamide challenge to be an imaging artifact (Fig. 1), and this patient was used as a normal control.

The patient’s left cerebral hemisphere was arbitrarily categorized as the “at-risk” brain tissue for the purpose of the PCT measurements, and compared to the right
Figure 1 The 3D time-of-flight (TOF) MRA demonstrated an occlusion of the petrous segment of the left internal carotid artery (arrow), corresponding to a lack of signal (arrow) on the partition images of the MRA. A flow void was however seen on the T2-weighted images (arrow), and the CTA following the acetazolamide challenge clearly demonstrated the petrous segment of the left internal carotid artery to be patent (arrow).

The average values for gray matter CBF, CBV, and MTT at baseline and 20 min after acetazolamide administration are reported in Table 1 both for the “normal” and “at-risk” brain tissues. CBF values (p < 0.001) and CBV values (p = 0.071) increased symmetrically in both hemispheres; MTT values were decreased symmetrically in both hemispheres (p = 0.015). Similar changes were observed in the watershed areas (CBF: +11%, p = 0.038; CBV: +15%, p = 0.023; MTT: −8%, p = 0.058) and also, though with lesser intensity, in the white matter.

Patient no.1

A 71-year-old male presented with one single episode of transient numbness bilaterally in his hands. CTA demonstrated a basilar artery occlusion, as well as an absent right posterior communicating artery (Fig. 3). The right and left PCA territories were considered to be at-risk brain tissue, with the right more at risk than the left; the bilateral ACA and MCA territories were considered to be normal brain tissue (Fig. 3).

The average values for CBF, CBV, and MTT in the gray matter both at baseline and 20 min after acetazolamide administration are reported in Table 1 both for the “normal” and “at-risk” brain tissues. CBF values (p < 0.001) and CBV values (p = 0.071) increased symmetrically in both hemispheres; MTT values were decreased symmetrically in both hemispheres (p = 0.015). Similar changes were observed in the watershed areas (CBF: +11%, p = 0.038; CBV: +15%, p = 0.023; MTT: −8%, p = 0.058) and also, though with lesser intensity, in the white matter.

Table 1 Comparing pre- and postacetazolamide PCT studies in the normal control subject, CBF and CBV values were increased symmetrically in both hemispheres; MTT values were decreased symmetrically in both hemispheres. This patient was considered as a normal control.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>‘‘At-risk’’</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CBF</td>
<td>42.75</td>
<td>55.76</td>
</tr>
<tr>
<td>CBV</td>
<td>3.47</td>
<td>3.76</td>
</tr>
<tr>
<td>MTT</td>
<td>4.91</td>
<td>4.05</td>
</tr>
</tbody>
</table>

Figure 2 The Circle of Willis in the normal control subject showed a patent anterior communicating artery. The bilateral posterior communicating arteries were absent. The patient’s left cerebral hemisphere was arbitrarily categorized as the “at-risk” brain tissue and compared to the right cerebral hemisphere, categorized as the “normal” brain tissue.

Figure 2 Le polygone de Willis chez le sujet témoin montre une artère communicante antérieure perméable. Les deux artères communicantes postérieures sont absentes. L’hémisphère cérébral gauche du patient fut arbitrairement catégorisé comme tissu cérébral « à risque » et comparé à l’hémisphère cérébral droit, catégorisé comme tissu cérébral « normal ».

MTT values were decreased symmetrically in both hemispheres (p = 0.015). Similar changes were observed in the watershed areas (CBF: +11%, p = 0.038; CBV: +15%, p = 0.023; MTT: −8%, p = 0.058) and also, though with lesser intensity, in the white matter.

Tableau 1 Chez le sujet témoin, après acétazolamide, les valeurs de débit et de volume sanguin cérébral augmentent symétriquement dans les deux hémisphères ; les valeurs de temps de transit moyen diminuent symétriquement dans les deux hémisphères.
administration are reported in Table 2 for the normal and at-risk brain tissues. At 20 min postacetazolamide administration, CBF values were decreased in the at-risk brain tissue (p = 0.023) and increased in the normal brain tissue (p < 0.001); MTT values were increased in the at-risk brain tissue (p = 0.038) and decreased in the normal brain tissue (p < 0.001); CBV values remained relatively stable (p = 0.233). Similar trends were observed in the watershed areas; similar trends were also recorded in the white matter, but of lesser intensity.

**Patient no.2**

A 38-year-old female presented with several episodes of slurred speech and transient numbness of her left arm and face. CTA demonstrated a stenosis in the right supraclinoid carotid artery, as well as an absence of the A1 segment of the right ACA and bilateral absence of the posterior communicating arteries. The right MCA territory was considered as at-risk brain tissue; the remaining brain parenchyma was considered as normal brain tissue.

The average values for gray matter CBF, CBV, and MTT at both baseline and 20 min after acetazolamide administration for the normal and at-risk brain tissues are reported in Table 3. From pre- to postacetazolamide challenge, CBF values decreased in the at-risk brain tissue (p = 0.038) and increased in the normal brain tissue (p < 0.001); both MTT values (p = 0.006) and CBV values (p = 0.004) increased in the at-risk brain tissue. Similar changes were observed in the watershed areas and also in the white matter, but of lesser intensity.

**Table 2** Comparing pre- and postacetazolamide PCT studies in Patient no.1, CBF values were decreased in the at-risk brain tissue and increased in the normal brain tissue; MTT values were increased in the at-risk brain tissue and decreased in the normal brain tissue; CBV values were relatively stable.

<table>
<thead>
<tr>
<th>Normal</th>
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<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CBF</td>
<td>47.19</td>
</tr>
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<td>CBV</td>
<td>3.60</td>
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<tr>
<td>MTT</td>
<td>4.58</td>
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</tbody>
</table>

**Table 3** Comparing pre- and postacetazolamide PCT studies in Patient no.2, CBF values were decreased in the at-risk brain tissue and increased in the normal brain tissue; both MTT and CBV values were increased in the at-risk brain tissue.

<table>
<thead>
<tr>
<th>Normal</th>
<th>“At-risk”</th>
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<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CBF</td>
<td>46.25</td>
</tr>
<tr>
<td>CBV</td>
<td>3.23</td>
</tr>
<tr>
<td>MTT</td>
<td>4.19</td>
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</table>
Patient no. 3

A 67-year-old male presented with repeated, frequent episodes of acute right-sided weakness and speech difficulty. CTA examination demonstrated a complete left internal carotid occlusion at the cervical level, as well as an absence of the right posterior communicating artery and the P1 segment of the right PCA at the intracranial level (Fig. 5). Based on these findings, the left MCA territory was considered as the at-risk brain tissue; the remaining brain parenchyma was considered as normal brain tissue (Fig. 5).

The average values of gray matter CBF, CBV, and MTT both at baseline and 20 min after acetazolamide administration for normal and at-risk brain tissues are reported in Table 4. After acetazolamide administration, CBF values decreased in the at-risk brain tissue ($p = 0.012$) and increased in the normal brain tissue ($p = 0.009$); MTT values ($p < 0.001$) and CBV values ($p = 0.007$) significantly increased in the at-risk brain tissue. Similar changes were noted in the watershed areas and white matter, though of lesser intensity in the latter.

Table 4 Comparing pre- and postacetazolamide PCT studies in Patient no. 3, CBF values were decreased in the at-risk brain tissue and increased in the normal brain tissue; MTT values were increased, and CBV values significantly increased in the at-risk brain tissue.

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<tr>
<th></th>
<th>Normal</th>
<th>&quot;At-risk&quot;</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CBF</td>
<td>38.99</td>
<td>62.90</td>
</tr>
<tr>
<td>CBV</td>
<td>3.29</td>
<td>2.97</td>
</tr>
<tr>
<td>MTT</td>
<td>5.07</td>
<td>2.86</td>
</tr>
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</table>

Figure 5 Patient no. 3 has a complete left internal carotid occlusion at the cervical level. The Circle of Willis shows an absence of the left posterior communicating artery (PCA) and the P1 segment of the right PCA at the intracranial level. The left middle cerebral artery (MCA) territory was considered as the at-risk brain tissue; the remaining brain parenchyma was considered as the normal brain tissue.

Figure 5 Le patient no 3 avait une occlusion complète de l’artère carotide interne gauche dans son segment cervical. Le polygone de Willis montre une absence de l’artère communicante postérieure gauche et du segment P1 de l’artère cérébrale postérieure droite. Le territoire alimenté par l’artère cérébrale moyenne gauche fut considéré comme tissu cérébral à risque ; le reste du cerveau fut considéré comme tissu cérébral normal.

The different patterns CBF, CBV and MTT changes from pre- to postacetazolamide administration observed in these patients with chronic cerebrovascular disease of increasing severity are summarized in Figs. 6—8.

Of note, the standard deviation on the CBF values was in the range of 10—15% in the normal brain tissue and in the range of 15—20% in the at-risk brain tissue.

Figure 6 Relative changes in CBF values (postacetazolamide values compared to pre-acetazolamide values) in the at-risk brain tissue, in the normal control subject and in the three patients with chronic cerebrovascular disease of increasing severity. CBF decreased in at-risk brain tissue in all patients, but was not discriminative of the severity of patients’ symptoms.

Figure 6 Changements en pourcentage des valeurs de débit sanguin cérébral (valeurs après acétazolamide comparées aux valeurs avant acétazolamide) dans le tissu cérébral à risque chez le sujet témoin et chez les trois patients avec des conditions cérébrovasculaires de sévérité croissante. Le débit sanguin cérébral diminue dans le tissu à risque de tous les patients. Toutefois, le degré de diminution ne permet pas de distinguer entre les différents degrés de sévérité des symptômes présentés par les patients.
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Figure 7 Relative changes in CBV values (postacetazolamide values compared to pre-acetazolamide values) in the at-risk brain tissue, in the normal control subject and in the three patients with chronic cerebrovascular disease of increasing severity. CBV change after acetazolamide in patients nos.1 and 2 was small and not significantly different from the normal control subject; CBV increased significantly only in patient no.3, who had the most severe symptoms.

Figure 7 Changements en pourcentage des valeurs de volume sanguin cérébral (valeurs après acétazolamide comparées aux valeurs avant acétazolamide) dans le tissu cérébral à risque chez le sujet témoin et chez les trois patients avec des conditions cérébrovasculaires de sévérité croissante. Les valeurs de volume sanguin cérébral chez les patients n°1 et 2 n'étaient pas différentes de celles observées chez le sujet témoin ; les valeurs de volume sanguin cérébral étaient augmentées seulement chez le patient n°3 qui avait les symptômes les plus sévères.

Discussion

In this article, we report the results of PCT-based acetazolamide challenges in one normal control subject and three patients with clinical histories clearly suggestive of declining cerebrovascular reserves (no.1 with a single TIA, no.2 with several TIAs, no.3 with multiple, prolonged TIAs). We used each patient’s clinical severity as a reference with which to compare the PCT data. We identified CBF, CBV and MTT changes from pre- to postacetazolamide administration that differed between patients with chronic cerebrovascular disease of increasing severity. In short, after administration of acetazolamide, CBF decreased in at-risk brain tissue in all patients, but was not discriminative based on the severity of patients’ clinical symptoms. CBV change after acetazolamide in patients nos.1 and 2 was small and not significantly different from that of the normal control subject; CBV increased significantly only in patient no.3, who presented with the most severe symptoms. MTT was the most discriminative parameter, decreasing after acetazolamide in the normal control subject and increasing in proportion to the severity of the symptoms in the patients.

Interestingly, baseline PCT values, prior to the administration of acetazolamide, also showed distinct patterns in patients with differing symptom severities (Table 5). Again, MTT was the most discriminative parameter, gradually increasing in the patients 1 through 3, from 4.5 to 8.1 s. Other PCT markers varied as follows: baseline CBV was high in patient no.2. This is likely the result of an attempt to maintain CBF at a normal level (→ CBF = ↑ CBV / ↑ MTT) by cerebral vascular autoregulation and corresponds with the consumption of some of the cerebrovascular reserve [1]. In patient no.3, increased MTT at baseline is so marked

<table>
<thead>
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<th>Table 5</th>
<th>Baseline, preacetazolamide PCT values of CBF, CBV and MTT parameters.</th>
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<tbody>
<tr>
<td><strong>At Risk</strong> Pre-Acetazolamide</td>
<td>Normal</td>
</tr>
<tr>
<td>CBF</td>
<td>↑</td>
</tr>
<tr>
<td>CBV</td>
<td>↑</td>
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<tr>
<td>MTT</td>
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that even the high CBV is insufficient to prevent a decrease in baseline CBF, likely corresponding to an exhaustion of the cerebrovascular reserve even before administration of acetazolamide. These static, baseline patterns could potentially be used to assess the cerebrovascular reserve without recourse to any dynamic challenge test, such as acetazolamide challenges.

In conclusion, we recommend that interpretation of acetazolamide challenges using PCT start with determination of potential at-risk brain tissue by identification of the site of stenosis/occlusion and review of the anatomy of the Circle of Willis. Then, the change in MTT in response to acetazolamide in the at-risk tissue should be measured as the parameter most closely correlated to the degree of impairment in cerebrovascular reserve, as assessed by clinical history. Finally, attention should be paid to the baseline pre-acetazolamide PCT values, because MTT may reveal a static indicator of compromised cerebrovascular reserve in at-risk territories. Further studies should investigate larger series of patients to determine PCT parameter thresholds that would allow for the identification of a sufficient degree of cerebrovascular reserve compromise to warrant bypass surgery.

Références