Perfusion CT to quantify the cerebral vasospasm following subarachnoid hemorrhage

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Available online 22 April 2010

KEYWORDS
Cerebral angiography; Perfusion computed tomography; Subarachnoid hemorrhage; Vasospasm

Summary

Background and purpose. — After subarachnoid hemorrhage (SAH), vasospasm is frequent and increases the risk of stroke and poor clinical outcome. The purpose of this study was to identify the best perfusion parameters in perfusion-CT (PCT) able to predict vasospasm diagnosed by angiography after SAH.

Methods. — Seventy-six patients with SAH were investigated by PCT and cerebral angiography. Using regions of interest (ROI) on parametric maps of mean transit time (MTT), time to peak (TTP), cerebral blood volume (CBV) and cerebral blood flow (CBF), PCT data were compared to an arteriographic score in two categories (severe vasospasm: ≥50% and non-severe vasospasm: <50%) for each artery. Best PCT predictors of the arteriographic score were tested using multiparametric logistic regression.

Results. — Among the 76 patients, PCT data were reliable in 65 patients. Twenty-seven patients had a severe vasospasm. Logistic regression showed that MTT was the best predictor of the arteriographic score. Using MTT, odds ratios having a vasospasm were superior to 3.1 and the occurrence of a vasospasm was accurately predicted in 78.5 to 100%, depending on the artery considered. However, no absolute value of the MTT could be identified to predict the occurrence of vasospasm. In fact, abnormal values of MTT ranged from 123 to 221% (m=146%) of the control values.

Discussion and conclusions. — PCT may accurately identify severe vasospasm and might be used as a convenient noninvasive imaging modality to monitor patients with SAH. When detected, severe vasospasm could be confirmed and managed using angiography and endovascular treatment, appropriately.

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Introduction

Subarachnoid hemorrhage (SAH) is the cause of 5% of strokes [1]. However, despite the relatively low incidence, the disability and loss of productive life years is comparable with brain infarction or hemorrhage [2].

Case fatality rates vary between 32 and 67% in population-based studies while 10–20% of all patients become disabled mostly due to delayed cerebral ischemia (DCI), related to vasospasm [3,4].

As prognosis could be improved by better neurointensive care management, focus should be pointed on first, early diagnostic of vasospasm, and second the risk evaluation of DCI induced by the vasospasm.

First, to detect the presence of vasospasm and its extent, imaging techniques such as transcranial Doppler (TCD) ultrasonography [5], computed tomography angiography (CTA), and cerebral conventional angiography [1,6] can be used. Conventional angiography remains the gold standard technique, but is associated with a risk of related stroke of 1 to 2% [7,8].

Second, perfusion computed tomography (PCT) may be a useful tool to identify ischemia as DCI is preceded by a decreased cerebral perfusion [9–12].

Among new neuroimaging modalities, PCT is now routinely performed in clinical practice, allowing rapid, minimally invasive, and quantitative evaluation of perfusion by generating parametric maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP). PCT has been proved to be a useful diagnostic tool to investigate brain perfusion related to vasospasm [9,12–17]. Small populations were studied and very few studies have been conducted on the diagnostic value of PCT compared to angiography [18–20].

PCT is probably a useful tool for predicting the risk of cerebral ischemia and could be potentially used to manage the patients with SAH.

Although severe vasospasm can decrease perfusion, it may not result in DCI [10], however, at an early stage, intensive care, both medical and endovascular therapy, has to be done in some cases to prevent ischemia and poor outcome.

Among the different PCT parameters, the goal of this study was to identify the best perfusion parameters in PCT corresponding to the vasospasm diagnosed by angiography after SAH, in order to select patients needing intensive special care to prevent DCI.

Patients and methods

Patients

We conducted a retrospective study on radiological data of 76 patients admitted in our institution with acute SAH.

All patients were investigated for vasospasm with serial neurologic examinations and TCD studies. Clinical condition was also recorded to know the hemodynamic and respiratory status which could interfere with brain perfusion data. Imaging protocol was usually scheduled around the 7th day postrupture, however, when the clinical findings were suspicious of early vasospasm, imaging exams were brought forward.

When present on angiography, severe vasospasm (≥ 50%) was treated with intra-arterial milrinone and/or endovascular balloon angioplasty, medical therapeutics (nimodipine, hypertensive therapy, etc), and external ventricular drainage when necessary.

Imaging protocol

The angiographies and PCT were performed within the first 10 days, after a mean delay of 7 days after SAH onset. Both angiography and PCT were performed the same day, the former following the latter, as a routine procedure. Angiography was performed as the gold standard technique to detect the presence and the extent of vasospasm, and PCT allowed analyzing its potential effect on brain perfusion, thus leading to specific and intensive treatment on selected patients.

Conventional angiography

Three or 4-vessels angiography was performed immediately after PCT via a transfemoral route under monitored sedation or general anesthesia, using a biplane digital angiographic unit (Neurostar® Siemens, Erlangen, Germany).

PCT

Using a 4-detector CT-scanner (Philips M × 8000), the protocol included a whole-brain unenhanced CT and a PCT at the level of the basal ganglia above the eye lenses. PCT consisted in four adjacent 5-mm-thick sections repeated every 2 s during 40 s, during a bolus of 40 mL of nonionic contrast agent iobitridol (XENETIX 300®, 300 mg/mL of iodine) administered via a 20-gauge line into an antecubital vein by using a power injector at 4 mL/sec. PCT was acquired at 90 kVp and 120 mAs.

Data processing and analysis

Conventional angiography

Angiographic data were reviewed independently by two interventional neuroradiologists (VL, PB), blinded to clinical and PCT data. Angiographic vasospasm was considered present when there was unequivocal narrowing of the arterial vessel lumen by visual inspection. Vasospasm was categorized as follows: none or moderate, 0 to 50% decrease in vessel diameter on the angigrams and severe > 50% decrease [9,10,21].

A simplified score for each artery was thus used to identify patients without vasospasm, with vasospasm below 50%, and with vasospasm above 50%.

Each intracranial artery ACA, MCA, and PCA was scored from 0 to 3, and the corresponding PCT data located at the level of the basal ganglia.

To estimate the severity of vasospasm and to avoid confusion with vessel hypoplasia, equivocal spastic arterial
segments were compared with the same ones on the angiography performed at initial admission.

PCT
Unenhanced CT were reviewed for grading the SAH according to the Fisher scale. PCT data were computed using Brain Perfusion®, Philips Medical Systems giving MTT, TTP, CBV, and CBF maps. For each parameter, quantitative values were extracted in cerebral arterial territories, by drawing five regions of interest (ROIs) on each hemisphere symmetrically located. The ROIs were defined in the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories, as well as in the junctional territories, the anterior junctional (AJ) between MCA and ACA territories, and posterior junctional (PJ) territories, between MCA and PCA territories.

The overall effective dose equivalent for the CT protocol was 1.84 mSv (1 mSv for unenhanced CT and 0.84 mSv for PCT).

Statistical analysis
Statistical analyses were conducted in two steps. First, to identify among the perfusion parameters measured across ROIs those significantly different between arteriographic score, ANOVA with repeated measures were performed, post-hoc comparisons using Student T-tests and Mann-Whitney tests were conducted when appropriate. Second, to determine the reliability of PCT to predict the arteriographic score, an unconditional logistic regression with stepwise backward selection was used. The probability value for exit in the logistic regression was set at 0.10. Adjusted odds ratios with 95% confidence intervals were calculated. Statistical procedures were performed using SPSS 15.0®, with significance set for \( p < 0.05 \).

Results

Patients population

Among the 76 patients initially managed, 11 patients were excluded from further analysis because of unreliable PCT by poor technique (mostly due to a poor bolus due to impaired hemodynamic), leaving 65 patients for the study, 24 men and 41 women with a median age of 50 years (range, 20–76 years). The CT-Fisher score was recorded as grade 4 (\( n = 25 \)), grade 3 (\( n = 10 \)), grade 2 (\( n = 3 \)), WFNS scores were grade 5 (\( n = 1 \)), grade 4 (\( n = 12 \)), grade 3 (\( n = 1 \)), and grade 2 (\( n = 26 \)). No difference could be detected between patients without any vasospasm from those with a vasospasm below 50%. Thus, data from both groups were further pooled and labeled as patients without severe vasospasm (<50%) in order to be compared to those from patients with severe vasospasm (≥50%).

Tables 1 and 2, and Fig. 1 summarize perfusion parameters across arterial territories. An illustrative case is shown Fig. 2.

Comparison of PCT and angiography in the diagnosis of vasospasm

Because of significant interaction between arteriographic score and ROI, post-hoc comparisons were conducted for all parameters in all ROI. Perfusion parameters significantly different between arteriographic score are listed in Table 2. In case of vasospasm, between-subjects comparisons showed mainly significant increase of MTT in proper arterial territory. Additionally, MTT in adjacent junctional territories were also increased in case of vasospasm of MCA. TTP and CBV were increased in case of vasospasm of ACA and left MCA. CBF were identical, but in case of vasospasm of the right PCA where a significant decrease was observed.

These parameters were further used in binary logistic regressions to predict the arteriographic score. Results of regressions are summarized in Table 1. For all arterial vasospasms but in left ACA, MTT measured in the proper arterial territory was identified as the best predictor of the arteriographic score. In left ACA vasospasm, MTT in the anterior junctional territory was the best predictor. Compared to the control values, MTT in severe vasospasm ranged from 123 to 217% (\( m = 149\% \)). No clear-cut value could be identified to simply predict the occurrence of vasospasm. At the arterial level and using MTT, the odds ratios to have a vasospasm ranged from 3.1 to \( > 10^6 \). The occurrence of a vasospasm was accurately predicted in 78.5 to 100%, depending on the artery considered.
Table 1: Occurrence of vasospasm and logistic regressions for each artery.

<table>
<thead>
<tr>
<th>Artery</th>
<th>Vasospasm ≥ 50%</th>
<th>Significant predictors (odds ratio [CI95%])</th>
<th>False positive/False negative (accuracy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right MCA</td>
<td>( n = 13 ) (20.0%)</td>
<td>( \text{MTT}_{\text{MCA}} (7.1 \ [2.4-20.4]) )</td>
<td>( n = 2 / n = 6 ) (87.7%)</td>
</tr>
<tr>
<td>Left MCA</td>
<td>( n = 8 ) (12.3%)</td>
<td>( \text{MTT}_{\text{MCA}} (4.3 \ [1.1-16.8]) )</td>
<td>( n = 1 / n = 2 ) (95.4%)</td>
</tr>
<tr>
<td>Right PCA</td>
<td>( n = 3 ) (4.6%)</td>
<td>( \text{MTT}_{\text{PCA}} (&gt; 10^6 \ [0-10^6]) )</td>
<td>( n = 0 / n = 0 ) (100%)</td>
</tr>
<tr>
<td>Left PCA</td>
<td>( n = 3 ) (4.6%)</td>
<td>( \text{MTT}_{\text{PCA}} (21.4 \ [1.3-358.9]) )</td>
<td>( n = 0 / n = 1 ) (98.5%)</td>
</tr>
<tr>
<td>Right ACA</td>
<td>( n = 22 ) (33.8%)</td>
<td>( \text{MTT}_{\text{ACA}} (6.7 \ [2.3-19.2]) )</td>
<td>( n = 4 / n = 10 ) (78.5%)</td>
</tr>
<tr>
<td>Left ACA</td>
<td>( n = 17 ) (26.2%)</td>
<td>( \text{MTT}_{\text{AJ}} (3.1 \ [1.6-6.3]) )</td>
<td>( n = 1 / n = 11 ) (81.5%)</td>
</tr>
</tbody>
</table>


\( ^a \) Occurrence of severe vasospasm among the patient sample (\( n = 65 \)).

\( ^b \) Significant predictors for vasospasm selected from regression analyses (odds ratio to have a vasospasm with a 95% confidence interval); mean value of the predictor ± standard deviation when vasospasm is detected.

\( ^c \) Performances of the model to predict severe vasospasm using significant predictors, with accuracy defined by: \( [(\text{true positive} + \text{true negative})/\text{total number of patient}] \).

Discussion

In the present study, we showed that using perfusion-CT (PCT), an increase of the mean transit time (MTT), ranging from 123 to 221% (\( \text{MTT} = 146\% \)), was the most accurate parameter to predict severe vasospasm in 78.5 to 100%, depending on the artery considered.

Screening for vasospasm

In clinical practice, vasospasm after SAH is routinely assessed using serial clinical examinations, TCD, and angiography within the first two week after the onset [1].

TCD is the most widely used to detect vasospasm noninvasively, although it has clear limitations. It has been reported

Table 2: Perfusion parameters significantly different across arteriographic score.

<table>
<thead>
<tr>
<th>ROI</th>
<th>MTT</th>
<th>TTP</th>
<th>CBV</th>
<th>CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper arterial territory(^a)</td>
<td>( \text{rMCA} (p &lt; 0.001))</td>
<td>( \text{IMCA} (p &lt; 0.001))</td>
<td>( \text{IMCA} (p = 0.01))</td>
<td>( \text{rPCA} (p = 0.01))</td>
</tr>
<tr>
<td>&amp; ( \text{LMCA} (p &lt; 0.001))</td>
<td>( \text{rACA} (p = 0.03))</td>
<td>( \text{rACA} (p = 0.003))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{rPCA} (p &lt; 0.001))</td>
<td>( \text{rPCA} (p = 0.02))</td>
<td>( \text{rPCA} (p = 0.02))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{rPCA} (p = 0.002))</td>
<td>( \text{LACA} (p = 0.001))</td>
<td>( \text{LACA} (p = 0.001))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior junctional(^b)</td>
<td>( \text{rMCA} (p = 0.01))</td>
<td>( \text{rACA} (p = 0.01))</td>
<td>( \text{rMCA} (p = 0.01))</td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{IMCA} (p = 0.001))</td>
<td>( \text{rACA} (p = 0.01))</td>
<td>( \text{IMCA} (p = 0.001))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{rACA} (p = 0.001))</td>
<td>( \text{rACA} (p = 0.001))</td>
<td>( \text{LACA} (p = 0.003))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{LACA} (p = 0.004))</td>
<td>( \text{LACA} (p = 0.004))</td>
<td>( \text{LACA} (p = 0.001))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior junctional(^c)</td>
<td>( \text{rMCA} (p = 0.02))</td>
<td>( \text{rPCA} (p = 0.02))</td>
<td>( \text{rPCA} (p = 0.01))</td>
<td></td>
</tr>
<tr>
<td>&amp; ( \text{IMCA} (p = 0.001))</td>
<td>( \text{rPCA} (p = 0.001))</td>
<td>( \text{rPCA} (p = 0.001))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( r \): right; \( l \): left; MCA: middle cerebral artery; PCA: posterior cerebral artery; ACA: anterior cerebral artery.

\( ^a \) Significant differences between patients without severe vasospasm and patients with severe vasospasm in the proper arterial territory of each artery.

\( ^b \) Parameters in anterior junctional ROI were computed for MCA and ACA.

\( ^c \) Parameters in posterior junctional ROI were computed for MCA and PCA.

\( d \) \( p \)-value of post-hoc comparisons.
as a highly specific but less sensitive test [22]. Moreover, in patients with disturbed autoregulation after SAH, induced hypertension could alter cerebral blood flow velocities [23]. Indeed, increased blood flow velocities measured by TCD do not correlate with brain perfusion values and cannot reliably distinguish between patients with vasospasm of various severity [24]. Finally, although TCD may detect severe vasospasm, reliable conclusion could only be obtained for MCA [25,26]. In our series, almost 60% of vasospasm occurred on the ACA. Thus, the use of TCD as a screening method is questionable.

In fact, many centers rely on cerebral angiography, an invasive technique, for the diagnosis of vasospasm [1]. Although angiography is the gold standard imaging modality to provide morphologic depiction of macroscopic vasculature, it does not allow quantitative analysis on cerebral perfusion.

Cerebral perfusion imaging

Cerebral perfusion abnormalities during vasospasm have already been studied with single-photon emission CT (SPECT) [27,28], positron emission tomography (TEP) [29,30], xenon enhanced CT [16,31], perfusion-weighted MRI [32]. Diffusion-weighted MR imaging has also been studied [33,34] and provided predictive markers of silent ischemic lesions and/or progression toward symptomatic ischemia in asymptomatic vasospasm [35].

However, those methods of investigation are not easily performed in daily clinical practice in patients with SAH requiring neurointensive care, long time procedure, and limited clinical access.

In such patients, CT is easy to perform in clinical practice, rapid, readily available, convenient, and a less invasive alternative to catheter angiography. Combining cerebral morphological examination, CT angiography and PCT, is a major interest to manage vasospasm [16].

PCT has been validated to study brain perfusion [36,37]. Moreover, it was reported to be a useful diagnostic tool to investigate vasospasm [9,13—20].

In our study, PCT values in patients with severe vasospasm, low CBF, high CBV and prolonged MTT, are in agreement with previous reports [13], especially concerning MTT as being the most sensitive parameter [16,19,20,38].
Illustrative case. A 46-year-old woman, WFNS 3 Fisher 4, presenting with a sylvian hematoma after SAH related to a right MCA ruptured aneurysm (clipped). Angiography performed 10 days after SAH shows vasospasm > 50% on the right MCA (black arrows). At PCT, MTT is increased in the right AJ (dotted arrow) (7.76 s), MCA (arrow) (8.87 s), and PJ (large arrow) territories (8.47 s), compared to the opposite AJ (5.29 s), MCA (4.68 s), and PJ territories (5.44 s). CBV is decreased on the right side with 34.54 ml/100 g/min in AJ, 40.89 in MCA, and 28.64 in PJ, while the values are normal in the opposite territories. CBV is only increased in the right MCA with 6.05 ml/100 g.

Unreliable values may occur when vasospasm is severe, as arterial input function cannot be properly selected, thus leading to irrelevant data; however, when it happens, this should definitely lead to angiography for prompt endovascular treatment. In acute stroke patients, the selection of different arterial input function has been demonstrated to have no significant effect on PCT results for an individual patient [39].

We acknowledge that the imaging technique has some limitations. PCT consisted of four slices located at the level of the basal ganglia with limited coverage (in this study only 2 cm). The brain perfusion analysis thus under diagnosed potential delayed perfusion on distal territories. However, currently, the use of increased detectors leads to expanded volume coverage.

MTT

The most accurate PCT parameter to predict angiographic vasospasm was MTT. No clear-cut value could be pointed out, contrary to a previous study, which reported a threshold at 6.4 s as the most accurate parameter for the diagnosis of angiographic vasospasm [19]. The lack of clear-cut value is in agreement with other studies [13–16]. Some studies were conducted with visual observation only [18,20].

Compared to the control values, MTT increased from 123 to 221% (m = 146%). An increase of the MTT over 20% than the mean (corresponding to 120% of the control MTT) has been shown to indicate the progression of cerebral vasospasm, and patients with vasospasm-related infarcts exhibited a MTT more than 47% greater than the mean value [16]. In diffuse vasospasm, the junctional territories, so-called watershed area, are the first involved. Although higher MTT values were recorded in those areas, they were non-significant, because of overlapping MTT values both in the vasospasm and no-vasospasm groups, the latter showing physiological prolonged values compared to proper territory. Nevertheless, close attention should be paid to those critical border areas since they are the first to be affected in diffuse vasospasm.

TTP

TTP values were not significantly higher in the vasospasm group. Indeed, TTP is not a discriminative parameter, as being calculated directly without any arterial input reference, opposed to MTT. Consequently, TTP is very sensitive to extracerebral or precerebral variables, such as cardiac function, aortic and aortic arch branch vessel stenosis and occlusion, or even variable position of the arm with variable impingement effect on the intravenous line where the iodinated contrast material bolus is injected for the PCT examination.

CBV and CBF

Differences between CBV and CBF reflect various moments in the timecourse of stroke and highlight vascular autoregulation. CBV was not discriminative between patients with and without vasospasm, as reported previously [38]. The overall higher CBV values in patients with vasospasm were related to preservation of the autoregulation, resulting in normal or increased CBV values [40]. Conversely, declining CBV indicates impaired autoregulation. Thus, low CBV is only observed in areas of infarction, which is seen in a minority of vasospasm cases at that stage, making CBV inappropriate as a sensitive screening parameter for vasospasm. As previously reported [16], higher MTT may be a prerequisite for cerebral vasospasm.
while CBV and CBF should be considered simultaneously.

In the vasospasm-group, aneurysmal rupture mainly occurred in Acoms and MCA arteries with subsequently more focal vasospasm preferentially located within both ACA and AJ territories, as well as left MCA territory, leading to significantly higher CBV results involving the whole anterior cerebral circulation and similarly the left MCA territory.

Despite CBF seemed decreased in patients with vasospasm, it was not significant because changes occurred in patients who both later experienced delayed cerebral ischemia or recovery from vasospasm without ischemia. Differences in CBF is thus found depending on the level of vasospasm which varies with the time course. Indeed, significance was reached in the right PCA territory in few patients who presented delayed ischemia. Furthermore, as PCT was performed at early stage of vasospasm, no major decreasing CBF had yet occurred.

Angiographic vasospasm below 50% had no significant effect on brain PCT in our study. Notably in normal conditions, CBF values were usually overestimated in MCA territory due to cortical vessels included in the ROIs improving the values of CBV, and consequently, the CBF ones. Conversely, CBF was usually underestimated in ACA territory because of more inclusion of white matter than in MCA territory, and white matter has actually been proved to show significant lower CBF and CBV than grey matter [13].

Dosimetry

Low kVp and mAs were used for PCT acquisition [41] with an effective dose (2.0–3.0 mSv) slightly higher than that required for routine head CT (1.5–2.5 mSv). Irradiation remained reasonable regarding conventional angiography.

Potential impact on vasospasm management and conclusion

As cerebral vasospasm is one of the major complications of SAH, and remains the main cause of delayed brain ischemia, adequate therapy is mandatory.

Our study showed the accuracy of PCT to diagnose severe vasospasm. To avoid performing angiography to patients without vasospasm, and because of the relatively low specificity of MTT, combining PCT to CTA would be of main interest [19,38] in reducing false-positive results. Then, one may suggest that conventional angiography could be performed only when vasospasm is suspected on clinical and CT data to discuss endovascular treatment. Confirmatory angiography for vasospasm could be avoided if the PCT study is negative. PCT should finally be proposed in all patients with SAH as an accurate screening method to select those who may need an active therapy.

Conflict of interest

None.

Acknowledgments

We gratefully acknowledge Cedric Mendoza and Patrice Jousse for their precious help in data collecting and editing figures.

References

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