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B. J. Shin

N. Anumula

S. Hurtado-Rua

P. Masi

R. Campbell

See next page for additional authors

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Authors
B. J. Shin, N. Anumula, S. Hurtado-Rua, P. Masi, R. Campbell, R. Spandorfer, A. Ferrone, T. Caruso, A. Gupta, P. C. Sanelli, and +2 additional authors
Does the location of the arterial input function affect quantitative CTP in vasospasm patients?

Benjamin J. Shin, MD,1 Nikesh Anumula, MD,1 Sandra Hurtado-Rúa, PhD,2 Paul Masi, BS,1 Ranita Campbell,1 Robert Spandorfer,1 Austin Ferrone,1 Thomas Caruso,1 Justin Haseltine,1 Christopher Robinson,1 Ajay Gupta, MD,1 and Pina C. Sanelli, MD MPH1,2

1Department of Radiology, Weill Cornell Medical College/NewYork-Presbyterian Hospital New York, NY
2Department of Public Health, Weill Cornell Medical College/NewYork-Presbyterian Hospital New York, NY

Abstract

Background and Purpose—To determine the effect on quantitative CTP data when the arterial input function (AIF) location is distal to significant vasospasm in aneurysmal SAH patients.

Materials and Methods—A retrospective study of aneurysmal SAH patients admitted from 2005 to 2011. Inclusion criteria were the presence of at least one ACA or MCA vessel with significant vasospasm (≥50% narrowing) and at least one of these vessels without vasospasm (<50% narrowing), as determined by concurrent CTA. Each CTP dataset was post-processed 4 separate times using standardized methods with only varying the selection of the AIF location in the ACA and MCA vessels. For each of the 4 separately processed exams for each patient, quantitative data for CBF, CBV and MTT was calculated by ROI sampling the vascular territories. Statistical analysis was performed using a linear mixed-effects model.

Results—A total of 112 uniquely processed CTP levels were analyzed in 28 patients (mean age 52 years; 24 women and 4 men) recruited from January 2005 to December 2011. The average Hunt-Hess score was 2.89 ± 0.79. The average time to CTP from initial presentation was 8.2 ± 5.1 days. For each vascular territory (right/left ACA, MCA, PCA), there were no significant difference between the quantitative CBF, CBV, and MTT generated by AIF locations distal to significant vasospasm compared to non-vasospasm vessels (p>0.05).

Conclusion—AIF placement distal to an artery in significant vasospasm does not affect the quantitative CTP data in the corresponding vascular territory or any other vascular territory in aneurysmal SAH.

Keywords

Arterial Input Function; Aneurysmal Subarachnoid Hemorrhage; CT Perfusion; Vasospasm

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Introduction

In recent years, there has been increasing use of CTP imaging in aneurysmal subarachnoid hemorrhage (aSAH) patients to evaluate for vasospasm. Several studies have reported CTP as a valuable tool to detect perfusion deficits related to vasospasm, described as focal areas of CBF reduction and/or MTT prolongation.\(^1\)\(^-\)\(^6\) In order to obtain the CBF, MTT and CBV maps, post-processing of the acquired dataset is performed. Deconvolution-based post-processing algorithms require selection of an arterial input function (AIF) to represent the actual injection rate of contrast as time-series data during its first pass in the artery. The mathematical algorithm “deconvolves” this arterial attenuation curve from the tissue attenuation curve to compute an impulse residue function (IRF). Based on the IRF curve, CBF is calculated as the height of this curve, CBV is the area under the curve, and MTT is the difference from the post-enhancement and pre-enhancement time-points.

Given the critical role of the AIF for generation of accurate CTP data, several studies have evaluated the effect of varying the AIF location in acute stroke patients.\(^7\)\(^-\)\(^9\) These studies revealed no significant difference in the quantitative CTP data with AIF selection ipsilateral or contralateral to the side of MCA vessel occlusion in either the ACA or MCA segments. However, AIF selection distal to an embolus revealed significant differences in the quantitative CTP data recommending avoiding its placement.\(^9\) It is unclear to what extent these findings are applicable to aSAH patients, since vasospasm results in narrowing rather than abrupt occlusion of the cerebral arteries. When significant vasospasm (≥50% narrowing) is present, perfusion deficits have been reported in the corresponding vascular territories\(^1\),\(^2\) supporting the hypothesis that AIF selection distal to severe vasospasm could potentially affect quantitative CTP data. To-date, there are no reports in the literature evaluating AIF placement in vasospasm. The purpose of this study is to determine the effect on quantitative CTP when the AIF location is distal to significant vasospasm in aSAH patients.

Materials and Methods

Study Design

A retrospective study of consecutive aSAH patients enrolled in a prospective clinical trial was performed to compare quantitative CTP data when the AIF location is distal to significant vasospasm (AIF\(_{VSP}\)) versus without vasospasm (AIF\(_{non-VSP}\)). Patients were enrolled in an IRB-approved clinical trial at our institution from January 2005 to December 2011. aSAH was diagnosed by NCCT, CTA, DSA, and/or cerebrospinal fluid analysis. The following inclusion criteria were applied in this study in order to compare quantitative CTP data when post-processing occurs with AIF\(_{VSP}\) and AIF\(_{non-VSP}\) within each patient: (1) CTA performed at the same time as CTP to determine which vessels were in vasospasm at the time of CTP acquisition, (2) presence of significant arterial narrowing (defined as ≥50%) related to vasospasm on CTA in at least one first-order segment of the ACA or MCA, and (3) absence of significant vasospasm on CTA in at least one first-order segment of the ACA or MCA. The exclusion criteria were: (1) CTP with extreme patient motion or inadequate contrast bolus in which post-processing could not be performed, and (2) CTP performed following treatment for vasospasm.

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Retrospective chart review was performed to collect demographic data on the study population, including age, gender, Hunt Hess grade, ruptured aneurysm location, and the day CTP was performed following aneurysm rupture.

**CTA Scanning and Interpretation**

CTA of the head was performed using a standard scanning protocol at our institution with GE Lightspeed or Pro-16 scanners (General Electric Medical Systems, Milwaukee, WI). The scanning parameters were 140 kVp and 370 mA at 0.625 mm thickness. A total of 90 mL of nonionic iodinated contrast was administered intravenously at 4 mL/s using a power injector. Standardized maximal intensity projection (MIP) images were reconstructed in the coronal, sagittal and axial planes.

CTA was used to determine the angiographic criteria for proximal vasospasm of the first-order cerebral vessels (A1 and M1 segments) based on the arterial luminal narrowing compared with the normal parent vessel and comparison with baseline CTA performed on admission. Based on published data, significant vasospasm was defined as ≥50% narrowing for resulting in perfusion deficits\(^1,2\), while no significant vasospasm was defined as <50% narrowing. CTA exams were interpreted by two observers, a neuroradiologist who performed the clinical interpretation (with 7–27 years experience) and another neuroradiologist (with 3 years experience) blinded to all clinical and imaging information. For disagreements, a third neuroradiologist (with 11 years experience) independently reviewed the exam in a blinded fashion.

**CTP Scanning, Post-Processing and Data Collection**

CTP was performed during the typical time-period for vasospasm between days 6–8 following aneurysm rupture. There is a standard scanning protocol for CTP at our institution using GE Lightspeed or Pro-16 scanners (General Electric Medical Systems) with cine 4i scanning mode and 45 second acquisition at 1 rotation per second using 80 kVp and 190 mA. A scanning volume of 2.0 cm was used consisting of 4 slices at 5.0 mm thickness with its inferior extent selected at the level of the basal ganglia, above the orbits, to minimize radiation exposure to the lenses. Approximately 45 mL of nonionic iodinated contrast was administered intravenously at 5 mL/s using a power injector with a 5 second delay.

Post-processing of the acquired dataset into CBF, CBV and MTT maps was performed on a GE Advantage Workstation using CTP software version 3.0 employing a deconvolution method. The post-processing technique was standardized for all patients according to recommended guidelines\(^10\) selecting the venous function as the superior sagittal sinus. While maintaining all post-processing parameters constant, each CTP dataset was post-processed four times by only varying the AIF location in the A2 segment of the right and left ACA and M2 segment of the right and left MCA (Figure 1). Placement of the AIF in the right and left-sided A2 and M2 segments was performed by a neuroradiologist (with 11 years experience) based on the concurrent CTA.

Quantitative analysis was conducted using a standardized method with contiguous ROI placement, measuring 157 mm\(^2\), sampling the cerebral cortex. Each CTP slice in each functional map (CBF, MTT, and CBV) had up to 24 ROIs distributed in the following
Statistical Analysis

A power analysis was performed to determine the sample size needed for this study design analyzing quantitative CTP data from six vascular territories (right and left-sided ACA, MCA and PCA) within each patient. Bonferroni adjustments were done for multiple comparisons such that the significance level (alpha) remained at 0.05. An effect size for CBF of 5 mL/100gm/min was used, indicating that the study would be adequately powered to detect a mean CBF difference of 5 units (per vascular territory) between the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data. This more conservative approach using a 5 unit difference in CBF may not necessarily be clinically significant, but is important in ensuring that the study design would detect small differences between AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data. The remaining parameters in the power analysis (mean, standard deviation) were based on pilot data. The sample size calculation was performed using PASS 2008, version 8.0.13. All tests were performed as 2-tailed. A sample size of 112 CTP levels (28 patients) achieves 90% power with a significance level (alpha) of 0.05.

Quantitative analysis of the CTP parameters was performed using a linear mixed-effects model. The response variable was CBF and the fixed effects in the model were vascular territory, AIF location and AIF status (AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP}). Subjects were included as random effects to account for multiple measures per subject. Contrasts to examine differences in CBF values in the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data by vascular territory and AIF location were reported along with their 95% confidence intervals (CI). Overall, this model accounts for inter-subject variability, variability in the number of vasospasm and non-vasospasm vessels amongst patients, variability in the number of measurements amongst patients, and missing data. Importantly, analysis for all six vascular territories can be performed using this single fitted model. Similar models were fit for the CBV and MTT analysis. Statistical analysis was performed by a biostatistician and conducted using R: A Language and Environment for Statistical Computing, R Development Core Team, Vienna, Austria, 2011, http://www.R-project.org.

Results

Study Population Characteristics

A total of 28 consecutive patients with aSAH were included in this study in order to achieve sufficient power for statistical analysis. The mean age is 52 years old (SD ± 11 years). There were 86% (24/28) female and 14% (4/28) male patients. Table 1 demonstrates the characteristics of the study population.

A total of 112 post-processed CTP levels were derived from the 28 patients; each patient’s acquired data was repeatedly post-processed four times by only varying the AIF location (right and left-sided A2 and M2 segments). Analysis was performed at the level of the 6 territories: approximately 6 ROIs in ACA, 12 ROIs in MCA and 6 ROIs in PCA. For accurate comparison of the quantitative CTP data derived from each of the 4 different AIF locations, an ROI template was created for each patient to replicate the exact size and location of the ROI sampling at each CTP level.
vascular territories (right and left-sided ACA, MCA and PCA) resulting in 672 territories for each CBF, CBV and MTT analysis.

**Quantitative CTP analysis by AIF location**

Figure 2A demonstrates the mean and 95% CI of the quantitative CTP data for all vascular territories in both the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data for each AIF location. There is no statistically significant difference in the quantitative CBF, CBV and MTT data between AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} (p>0.05) for any of the AIF locations.

**Quantitative CTP analysis by vascular territory**

Figure 2B demonstrates the mean and 95% CI of the quantitative CTP data for each vascular territory in both the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data. There is no statistically significant difference in the quantitative CBF, CBV and MTT data between AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} (p>0.05) for any vascular territories.

**Quantitative CTP analysis by AIF location and its corresponding vascular territory**

An additional analysis was performed to evaluate the quantitative CTP data for the MCA and ACA territories when the AIF is located in its supplying artery in both the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data (Table 2). There is no statistically significant difference in the quantitative CBF, CBV and MTT data between the AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data for each vascular territory.

**Discussion**

Given its reported high sensitivity and specificity to detect perfusion abnormalities thought to occur in vasospasm,\textsuperscript{1,3–6} CTP has been increasingly used in aSAH patients. Several studies have also suggested quantitative threshold values for CBF and MTT to determine perfusion deficits for management and treatment of vasospasm.\textsuperscript{1,3,4,6} However, generation of accurate and reproducible quantitative CTP data relies on selecting an appropriate AIF. Utilizing a standard AIF placement, such as the A2 segment, in post-processing CTP data may further improve its reproducibility for comparison.\textsuperscript{7} Standardization of the AIF location in aSAH patients with vasospasm is challenging given the diffuse and variable pattern of vasospasm.\textsuperscript{1,3–6}

A review of the literature reveals several studies demonstrating the robustness of various AIF locations in patients with acute stroke.\textsuperscript{7–11} These studies found that major variations in the AIF location had no significant effect on the quantitative CTP data.\textsuperscript{7,9–11} Additionally, the ACA and even the superficial temporal artery may be used as appropriate AIF locations in patients with acute stroke regardless of the cortical region affected which may assist in standardization of the AIF location.\textsuperscript{7,9–11} Furthermore, there is no significant difference in the quantitative CTP data when selecting an AIF location in the MCA or ACA segments ipsilateral or contralateral to the vascular territory with infarction.\textsuperscript{9,11} Importantly, placement of the AIF in a vessel distal to the thrombus has been shown to affect the quantitative CTP data\textsuperscript{9} by overestimating MTT and underestimating CBF values due to the marked delay or lack of contrast distal to the clot. It is physiologically plausible that marked
delay in contrast arrival distal to a vessel in significant vasospasm may also be applicable in aSAH patients, but to our knowledge has never been studied.

Significant vasospasm, defined as ≥50% arterial narrowing, has been found to result in perfusion deficits attributed to proximal vasospasm.1,2 These findings suggest that this degree of arterial narrowing is hemodynamically significant and potentially could result in delay of the contrast arrival in the distal vessel. The arterial attenuation curve distal to significant vasospasm has been shown to be diminished in height and prolonged along the time series in digital subtraction angiography.12 The effect of contrast bolus delay on the quantitative CTP parameters is the rationale of our study as delay in contrast is also seen in patients with significant vasospasm.13 Our study revealed no statistically significant difference in the quantitative CBF, CBV, or MTT data between AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data (Figure 3) according to AIF location and vascular territory. Furthermore, there was no quantitative difference in these CTP parameters in the ACA or MCA vascular territories when the AIF location was in its supplying artery with or without vasospasm. Similar to the acute stroke literature, our results suggest that there is no significant difference in the quantitative CTP data for different AIF locations. Additionally, there is no significant quantitative difference when the AIF placement is distal to significant vasospasm suggesting that the deconvolution-based algorithm is robust to alterations in the height and width of the arterial attenuation curve as seen in significant vasospasm. Similar findings were also found in acute stroke patients when AIF placement distal to the embolus was used with deconvolution-based algorithms with delay-insensitive techniques.9 Another possible explanation is that the delay in contrast arrival distal to vasospasm is not as severe as expected distal to an obstructing embolus.

These results have several potential implications for patient care in those centers utilizing CTP in aSAH patients. First, flexibility in selecting the AIF location in patients with vasospasm is valuable given its challenges with streak artifact from surgical clip or coils and motion degradation in this population. Second, it is not always known at the time of post processing the CTP if a vessel is in vasospasm when selecting the AIF location. Our study suggests that the presence of significant vasospasm does not have to be determined from CTA interpretation prior to selecting an AIF location for CTP post-processing. Third, given that many post-processing software have fully or semi-automated processing methods to rapidly generate CBF, CBV and MTT maps, our study supports the selection of variable AIF locations in the A2 or M2 segments by automated computer algorithms. Last, AIF placement is not a limiting factor in post-processing CTP data in patients with diffuse vasospasm.

There are several limitations in our study to be considered. We were not able to assess collateral circulation and communicating arteries with great certainty because these vessels were below the diagnostic threshold of the concurrent CTA. Documentation of the collateral circulation would have been helpful to further explore possible explanations why significant vasospasm does not affect the quantitative data especially since vasospasm has been shown to delay blood flow and collateral circulation can potentially help maintain perfusion, as seen in acute stroke.14–16 However, the effect of collateral flow on perfusion has not been well studied in vasospasm and remains uncertain. In addition, the posterior circulation and its territory were not analyzed in this study because many CTP in this study captured limited
areas of the posterior circulation. Finally, since no statistically significant difference was detected between AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} CTP data, the risk of our study being underpowered might be considered as a possible limitation. However, since we were statistically powered to detect differences that are even below the threshold of what many would not consider to be a clinically significant difference in CBF (5 units), this is unlikely to have affected the significance or validity of our findings.

**Conclusion**

AIF placement distal to an artery in significant vasospasm does not significantly affect the quantitative CTP data in the corresponding vascular territory or any other vascular territory in patients with aSAH. Therefore, vasospasm status should not necessarily influence the selection of the AIF location either in the ACA or MCA segments. This information may be helpful in selecting an AIF location in challenging aSAH patients with diffuse vasospasm, streak artifact from aneurysm repair and motion.

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**References**


Figure 1.
Examples of the standardized AIF locations selected according to the study protocol. The AIFs (red arrows) are placed in the right and left A2 and M2 segments of the ACA and MCA, respectively, within the same patient. The venous output function (blue arrows) is not varied and held constant within the same patient. The arterial attenuation curves (green) and venous attenuation curves (purple) generated by the respective arterial and venous functions are demonstrated to the right of each image. In this particular example, the AIF location in the left M2 segment is distal to significant vasospasm and demonstrates reduced height of its arterial attenuation curve.
Figure 2.
(A) Model-adjusted mean and 95% CI bars are displayed for the quantitative CBF, CBV and MTT data for all the vascular territories according to the AIF location. The dashed line represents the quantitative data when AIF_{VSP} was used for post-processing and the continuous line represents the quantitative data when AIF_{non-VSP} was used. (B) Model-adjusted mean and 95% CI bars are displayed for the quantitative CBF, CBV and MTT data for each vascular territory when the AIF is located distal to significant vasospasm versus no vasospasm. The dashed line represents the quantitative data when AIF_{VSP} was used for post-processing and the continuous line represents the quantitative data when AIF_{non-VSP} was used.

Figure 3.
Functional maps of CBF, CBV, and MTT using an AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} within the same patient. (A) Top row represents the CTP maps for the AIF location in an A2 segment without vasospasm in the proximal ACA. (B) Bottom row represents the CTP maps for the AIF location in an M2 segment distal to proximal vasospasm. There is no significant difference in the quantitative data between these two sets of CTP maps in this patient. In addition, the maps appear qualitatively similar with a small perfusion deficit in the left temporoparietal region.
### Table 1

Study population characteristics (n=28)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>52 ± 11</td>
</tr>
<tr>
<td>Gender: Female</td>
<td>86% (24/28)</td>
</tr>
<tr>
<td>Hunt-Hess Score (mean)</td>
<td>2.89 ± 0.79</td>
</tr>
<tr>
<td>Time to CTP Exam (mean days)(^\dagger)</td>
<td>8.2 ± 5.1</td>
</tr>
<tr>
<td>Aneurysm Site(^\ddagger)</td>
<td></td>
</tr>
<tr>
<td>Basilar</td>
<td>3.6% (1/28)</td>
</tr>
<tr>
<td>ICA</td>
<td>35.7% (10/28)</td>
</tr>
<tr>
<td>ACOM</td>
<td>14.3% (4/28)</td>
</tr>
<tr>
<td>ACA</td>
<td>3.6% (1/28)</td>
</tr>
<tr>
<td>MCA</td>
<td>32.1% (9/28)</td>
</tr>
<tr>
<td>PCOM</td>
<td>25% (7/28)</td>
</tr>
<tr>
<td>Multiple</td>
<td>25% (7/28)</td>
</tr>
<tr>
<td>First Order Cerebral Arteries(^*)</td>
<td></td>
</tr>
<tr>
<td>Significant vasospasm - AIF\textsubscript{VSP} (≥50% narrowing)</td>
<td>56</td>
</tr>
<tr>
<td>No significant vasospasm - AIF\textsubscript{non-VSP} (&lt;50% narrowing)</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^\dagger\) Time from initial diagnosis to CTP scanning.

\(^\ddagger\) Number of patients with an aneurysm at the specified site. Please note, total exceeds 100% as some patients had multiple aneurysms.

\(^*\) Two cerebral arteries could not be evaluated due to streak artifact and motion.
Table 2

Model-adjusted mean and 95% CI for CBF, CBV, and MTT data classified by the vascular territory and AIF location in its supplying artery in both AIF\textsubscript{VSP} and AIF\textsubscript{non-VSP} data.

<table>
<thead>
<tr>
<th>Vascular Territory</th>
<th>Quantitative CTP Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cerebral Blood Flow (\text{mL/100gm/min})</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>R ACA</td>
<td></td>
</tr>
<tr>
<td>RA2 AIF\textsubscript{VSP}</td>
<td>38.68</td>
</tr>
<tr>
<td>RA2 AIF\textsubscript{non-VSP}</td>
<td>42.11</td>
</tr>
<tr>
<td>R MCA</td>
<td></td>
</tr>
<tr>
<td>RM2 AIF\textsubscript{VSP}</td>
<td>60.99</td>
</tr>
<tr>
<td>RM2 AIF\textsubscript{non-VSP}</td>
<td>62.80</td>
</tr>
<tr>
<td>L ACA</td>
<td></td>
</tr>
<tr>
<td>LA2 AIF\textsubscript{VSP}</td>
<td>34.23</td>
</tr>
<tr>
<td>LA2 AIF\textsubscript{non-VSP}</td>
<td>37.73</td>
</tr>
<tr>
<td>L MCA</td>
<td></td>
</tr>
<tr>
<td>LM2 AIF\textsubscript{VSP}</td>
<td>53.09</td>
</tr>
<tr>
<td>LM2 AIF\textsubscript{non-VSP}</td>
<td>58.76</td>
</tr>
</tbody>
</table>

Abbreviations: ACA - anterior cerebral artery, MCA - middle cerebral artery, PCA - posterior cerebral artery, AIF - arterial input function.