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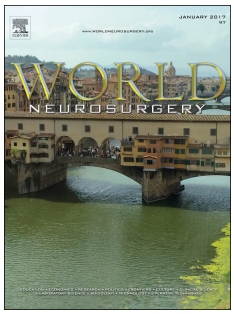

Repetitive CT perfusion for detection of cerebral vasospasm-related hypoperfusion in aneurysmal subarachnoid hemorrhage

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Repetitive CT perfusion for detection of cerebral vasospasm-related hypoperfusion in aneurysmal subarachnoid hemorrhage

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Short title: CT perfusion in subarachnoid hemorrhage

Keywords: cerebral vasospasm – subarachnoid hemorrhage – delayed cerebral ischemia – misery perfusion – CT perfusion parameters

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Abbreviation list

aSAH: aneurysmal subarachnoid hemorrhage
AUC: area under the curve
CBF: cerebral blood flow
CBV: cerebral blood volume
CI: confidence interval
CTP: CT perfusion
DCI: delayed cerebral ischemia
HU: Hounsfield units
MCA: middle cerebral artery
MTT: mean transit time
ROC: receiver operator characteristics
ROI: region of interest
SD: standard deviation
SVD: standard algorithm program
TTD: time to drain
TTP: time to peak

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Abstract

Background: Delayed cerebral infarction after aneurysmal subarachnoid hemorrhage (aSAH) still remains the leading cause of disability in patients that survive the initial ictus. It has been shown that CT perfusion (CTP) imaging can detect hypoperfused brain areas. The aim of this study was to evaluate if a single acute CTP examination at time of neurological deterioration is sufficient or if an additional baseline CTP increases diagnostic accuracy.

Methods: Retrospective analysis of acute and baseline (within 24 hours after aneurysm treatment) CTP examinations of patients with neurological deterioration because of vasospasm-related hypoperfusion. Patients without clinical deterioration during the vasospasm period served as controls. The following CTP parameters were analyzed for predefined brain regions: time to drain (TTD), mean transit time, time to peak, cerebral blood flow and volume.

Results: 33 patients with and 23 without neurological deterioration were included. Baseline CTP examination did not ameliorate diagnostic accuracy of the acute CTP examination in symptomatic patients. The same was true for inter-hemispheric comparison of perfusion parameters of the acute examination. The CTP parameter with the highest diagnostic yield was TTD of the symptomatic brain region (threshold value 4.7 sec, sensitivities 97 %, specificities 96 %).

Conclusions: Acute CTP examination in case of suspected vasospasm-induced neurological deterioration after aSAH has the highest diagnostic accuracy to detect misery perfusion. Additional baseline CTP is not needed. The most sensitive parameter to detect critically perfused brain areas is TTD.

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Introduction

In aneurysmal subarachnoid hemorrhage (aSAH) cerebral vasospasm remains the leading cause of disability in patients that survive the initial ictus and in whom the ruptured aneurysm has been secured [1-3]. The reported incidence of vasospasm-induced cerebral infarction is up to 44% [4-6]. For guidance of therapy, early diagnosis of evolving cerebral vasospasm and misery perfusion as well as exclusion of other possible causes for clinical deterioration are therefore crucial. In the past, various diagnostic methods for detection of cerebral vasospasms have been evaluated [7-16]. Because of its diagnostic accuracy and clinical applicability, computed tomography perfusion (CTP) imaging is more and more used in clinical practice. Reported sensitivities for detection of delayed cerebral ischemia (DCI) range from 20% to 95% with specificities higher than 66% [8, 9, 17, 18]. The diagnostic accuracy strongly depends on the perfusion parameter being used for analysis. Several studies have shown that mean transit time (MTT) and time to peak (TTP) show superior sensitivities and specificities than the parameters cerebral blood flow (CBF) and cerebral blood volume (CBV) [19-23]. A recent study confirmed these earlier findings and elaborated that the relatively new parameter TTD is even more effective to detect DCI [24]. TTD is defined as time to start + MTT and measures the time the contrast agent passes away from the analyzed voxel. Several studies evaluated threshold values for the above CTP parameters by either comparing hemispheric difference or absolute values of hypoperfused brain areas and reported no clear benefit of either method [19, 22]. The aim of this study was to evaluate if a single CTP at the time of neurological deterioration is sufficient or if serial CTP examinations are needed to reliably detect brain areas at risk for infarction and which CTP parameter is most appropriate.

Materials and Methods

This is a single-center retrospective case-control study of patients with aSAH treated at the University Hospital Bern, Switzerland. The institutional review board of the University

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Hospital Bern and the local ethics committee (Kantonale Ethikkommission Bern, Switzerland) gave approval for the access and use of the data collective with the intention for retrospective clinical research. Only patients aged >18 years and < 80 years were included.

Design

We retrospectively searched our prospectively conducted database for patients with aSAH admitted between January 2012 and December 2015. Clinical courses of all patients were evaluated carefully and patients with neurological deterioration due to cerebral vasospasms and patients with clinically stable course were extracted. Patients with deterioration caused by other pathologies such as hydrocephalus, infection, intracerebral bleeding, metabolic disturbances or epileptic seizures were excluded from the analysis. DCI was defined as acute occurring neurological deficit fulfilling the following criteria: decrease of Glasgow Coma Scale of at least 2 points and/or increase of the National Institutes of Health Stroke Scale (NIHSS) of at least 2 points. Out of this selection, only patients with CTP examination within 24 hours after aneurysm treatment (baseline CTP) and follow up CTP examination at time of acute neurological deterioration were included (acute CTP). Patients with clinically stable course, which underwent CTP examination within 24 hours after aneurysm treatment (baseline CTP) and follow up CTP examination during the vasospasm phase (day 5 to 14 after aSAH) served as controls. According to our treatment algorithm in patients with aSAH an early CTP examination is performed within 24 hours after aneurysm treatment for diagnosis of treatment associated abnormalities. During the follow-up period, additional CTP is performed in case of acute occurring neurological deficit or if indicated for other reasons by the treating physician.

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Imaging Protocol and data processing

CTP was performed using a 128-slice scanner (Somatom Definition Edge, Siemens Healthcare, Erlangen, Germany). In routine practice, our institute's perfusion images are planned in a supra-orbitomeatal vertical line. The perfusion images were obtained during application of 30 ml of intravenous contrast medium (Iomeron 400, Bracco Suisse SA, Manno TI, Switzerland) followed by a 30ml saline flush with 5 ml/s flow with a mechanical injector (Swiss Medical Care, Lausanne, Switzerland). The acquisition parameters of the CTP were: slice thickness 5.0 mm; matrix 512 × 512; FOV 20; total acquisition time 57 s by tube current-time product of 200 mAs; and tube voltage 80 kv. CTP resulted on average in a CTDI of 223 mGy and on average a dose-length product of 2630 mGy.cm. Automatic exposure control was not applied as it could affect the perfusion parameter [25, 26].

Quantitative analysis was done using a standard algorithm (SVD) program (syngo.via, Siemens Healthcare GmbH, Erlangen, Germany). Ten standard regions-of-interest (ROIs) were set on two rostro-caudal levels of the acquired CTP: a) centrum semiovale (Figure 1a) and b) 3rd ventricle (Figure 1b). At the level of the centrum semiovale 2 ROIs were symmetrically set in the vascular territory of the middle cerebral artery (MCA) (Figure 1a). At the level of the 3rd ventricle 6 ROIs were symmetrically placed in the vascular territory of the anterior cerebral artery, the MCA and the posterior cerebral artery (Figure 1b). Additionally, 2 ROIs were placed in the region of the basal ganglia (Figure 1c). For each marked ROI the parameters: MTT, TTP, TTD, CBF and CBV were automatically generated by the scanner software program (commercial perfusion package VPCT-Neuro, Siemens Healthcare, Forchheim, Germany). The recently into the software implemented parameter TTD describes the time of contrast medium washout. Specifically, TTD is defined as the sum of the delay between contrast medium injection and first cerebral arterial enhancement (also called "time to start") and MTT**.** The utilized deconvolution method and the calculation of the perfusion maps have been described in detail by Abels et al. [27]. Motion correction and 4D noise

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reduction options were applied as provided by the perfusion software. Hounsfield Units (HU)-based semi-automatic segmentation of the brain tissue was performed. Arterial input function was measured in the MCA; the venous outflow was taken from the superior sagittal sinus. Evaluation of perfusion map images was performed by one experienced neuroradiologist (WF), who was blinded to the clinical course of the examined patients.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 21.0 (IBM, Armonk, NW, USA). The Shapiro-Wilk normality test was used to test for normal distribution of data sets. The unpaired *t*-test was applied to test for significant differences of metric variables between the two groups. For comparison of CTP variables (MTT, TTP, TTD, CBV and CBF) in patients with DCI, the ROI corresponding to the clinically symptomatic brain area was defined. The same ROI was selected in the baseline CTP. In the clinically unaffected hemisphere the corresponding mirror ROI was selected from the baseline and acute CTPs. In patients without DCI, the ROI placed in the vascular territory of the left MCA at the level of the centrum semiovale was analyzed and compared to the mirror ROI of the right hemisphere and the corresponding ROIs of the baseline CTP respectively. Multivariate ANOVA for repeat measures was used to test for differences in perfusion parameters. Data are presented as mean ± standard deviation (SD). A p-value < 0.05 was considered statistically significant.

The diagnostic threshold values for the distinct perfusion parameters (absolute and for hemispheric differences at the time point of DCI as well as compared to the baseline CTP) were determined using receiver operator characteristics (ROC) curves. From the ROC curves, optimal threshold values to distinguish between patients with and without DCI were derived by seeking the best tradeoff between highest possible sensitivities and specificities. Determined sensitivities and specificities were then used to create likelihood ratio graphs to visualize diagnostic properties of the different CTP parameters.

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Results

Patients' clinical characteristics

One hundred sixty-five patients were evaluated for this study, of which 109 were excluded because they did not match the inclusion criteria or because of incomplete clinical data sets and/or incomplete/insufficient radiological data. Finally, 33 patients with DCI and 23 patients without DCI (control group) were enrolled. Table 1 shows clinical characteristic of patients with DCI and the control group. There was a tendency for a higher percentage of female gender and a higher WFNS and BNI score in the DCI group.

CT Perfusion parameters

Figure 2 a-c and Figure 3 a-b show MTT, TTP, TTD, CBF and CBV for both hemispheres of baseline and acute CTP examinations for patients with DCI and controls. In patients with DCI, MTT, TTP and TTD were significantly prolonged and CBF decreased compared to the not symptomatic hemisphere and to the baseline CTP. The changes of MTT, TTP and TTD were more prominent than the change of CBF. The unaffected hemisphere showed no changes of perfusion characteristics in the acute CTP compared to the baseline CTP both in patients with DCI and in controls.

Threshold values for predicting DCI

Table 2 shows diagnostic threshold values for distinct CTP parameters derived from the ROC analysis. Separate threshold values were calculated for the symptomatic hemisphere as well as the inter-hemispheric difference in the acute CTP and for the difference between the acute and baseline CTP investigations. The corresponding likelihood ratio graphs are shown in Figure 4 a-d. Overall, the CTP parameter with the highest sensitivity and specificity was absolute TTD of the symptomatic brain area in the acute CTP. The threshold value was 4.7 sec. Comparison with the contralateral side in the acute CTP or the same region in the baseline examination

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resulted in slightly lower sensitivities and specificities. The other parameters with good diagnostic properties were TTP and MTT. Whereas MTT showed similar area under the curve (AUC) values (confidence interval (CI) 95%) for the symptomatic side as well as the inter-hemispheric comparison in the acute CTP, TTP showed a slightly better diagnostic accuracy for inter-hemispheric differences than for the symptomatic side only in the acute CTP.

Discussion

In aSAH vasospasm-induced cerebral infarction still remains the leading cause of disability in patients that survive the initial ictus [1-3]. In our retrospective study we analyzed if a single CTP at time of neurological deterioration is sufficient to reliably detect critically hypoperfused brain areas or if an additional baseline CTP examination increases the diagnostic yield. In addition, the CTP parameters with the highest specificity and sensitivity were determined. Overall, additional baseline CTP examination did not ameliorate diagnostic accuracy of the acute CTP examination in symptomatic patients. The same was true for inter-hemispheric comparison of perfusion parameters of the acute examination. The CTP parameter with the highest diagnostic yield was TTD, followed by TTP and MTT.

Changes of systemic hemodynamic parameters in patients after aSAH in parallel to evolving cerebral vasospasms are a well-known phenomenon [28, 29]. Typically, an increase of systemic blood pressure can be observed, which is more pronounced in patients with more severe cerebral vasospasms [28]. Based on this phenomenon, one may expect systematic alterations of CTP examinations acquired in patients with vasospasms, e.g. global changes of CTP parameters involving also non-symptomatic brain areas. We therefore compared CTP examinations of patients with and without acute neurological deficit with a baseline CTP examination acquired before the onset of the vasospasm period. In patients with acute neurological deficit, there were no changes of CTP parameters in clinically asymptomatic

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brain areas between the baseline and the acute CTP examination found (Figure 2 a-c, Figure 3 a-b). The same was true for clinically asymptomatic patients. Hence, systemic alterations of hemodynamic parameters seem not to affect CTP examinations. This may be explained by two reasons. First, for CTP analysis arterial input function has to be determined. Generally, a basal cerebral artery (e.g. MCA) is selected for this purpose, which minimizes effects of systemic hemodynamics on measured CTP parameters. Second, cerebral autoregulation, if not impaired, maintains cerebral blood flow constant and may compensates for changes in systemic hemodynamics. Hence, a baseline CTP does not improve the diagnostic yield and is therefore not required. For clinical practice, this leads to a reduction of the number of transportations of critically ill patients from the intensive care unit to the neuroradiology department with possible harm of the patient during transportation, exposure of the patient to radiation and high costs [30, 31].

Of all evaluated CTP parameters, TTD was found to have the best diagnostic accuracy for detecting critical hypoperfusion in patients with acute neurological deficits (Table 2). TTD is a recently introduced deconvolution-based parameter describing the time of contrast medium washout. It is defined as the sum of the time from arterial enhancement to tissue enhancement (time to start) and MTT, being sensitive to hemodynamic disturbances. In our study, three conditions were analyzed: i) acute CTP - clinically symptomatic brain area, ii) acute CTP - inter-hemispheric difference and iii) difference between acute and baseline CTP examination. TDD showed for all three conditions excellent diagnostic accuracies (AUC 0.951 – 0.992). Highest diagnostic accuracy was found for absolute values of the clinically symptomatic brain area in the acute CTP (AUC 0.992, threshold value 4.7 sec, sensitivities 97 %, specificities 96 %; Table 2). This is well in line with a recent report from Othman et al.[24], which correlated volume perfusion CT maps with findings of cerebral angiography and found superior diagnostic accuracy for TTD compared to MTT, CBV and CBF. Since that study did not include patients with acute neurological deficit, no threshold values for TTD were derived.

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The other CTP parameters with good diagnostic accuracy were TTP and MTT. As for TTD, diagnostic accuracy was highest in the acute CTP examination for both parameters (Table 2). Comparison with the baseline CTP examination resulted in a lower diagnostic yield. In the acute CTP, MTT showed similar AUC values for the symptomatic brain region and for the inter-hemispheric comparison. TTP showed a slightly higher diagnostic accuracy for inter-hemispheric differences than for the symptomatic side only (Table 2). Earlier studies already showed high sensitivities and specificities for MTT and TTP for detecting misery perfusion in symptomatic patients [19, 22, 32, 33]. These studies did not yet evaluate the relatively new parameter TTD. Because of methodological and technical difference published threshold values for MTT and especially for TTP vary between studies [19, 22, 32, 33].

The findings of our study may help to facilitate diagnosis of DCI in neurologically not evaluable patients. This patient cohort poses one of the greatest challenges in clinical practice since most of the available monitoring tools are of limited value and may can miss misery perfusion.

The major limitation of this study is its retrospective design in a single center setting. Furthermore, only a relatively small cohort of patients was finally investigated and there were slight differences in characteristics between the group of patients with DCI and controls. The latter is a frequently encountered problem in studies about vasospasms after aSAB and reflects the different risk profile of these patient groups. To minimize bias, perfusion map images were analyzed by one experienced neuroradiologist, who was blinded to the clinical course of the examined patients.

In conclusion, our results show that acute CTP examination in case of vasospasm-induced neurological deterioration after aSAH has the highest diagnostic accuracy to detect misery perfusion and that baseline CTP is not needed. The most sensitive parameter to detect critically perfused brain areas during the vasospasm phase after aSAH is TTD.

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Declaration of interest: None

References

1. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007;369:306-318.
2. Adamczyk P, He S, Amar AP, Mack WJ. Medical Management of Cerebral Vasospasm following Aneurysmal Subarachnoid Hemorrhage: A Review of Current and Emerging Therapeutic Interventions. *Neurology research international* 2013;2013:462491.
3. Brathwaite S, Macdonald RL. Current management of delayed cerebral ischemia: update from results of recent clinical trials. *Translational stroke research* 2014;5:207-226.
4. Rabinstein AA, Friedman JA, Weigand SD, et al. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* 2004;35:1862-1866.
5. Vajkoczy P, Meyer B, Weidauer S, et al. Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study. *Journal of neurosurgery* 2005;103:9-17.
6. Weidauer S, Lanfermann H, Raabe A, Zanella F, Seifert V, Beck J. Impairment of cerebral perfusion and infarct patterns attributable to vasospasm after aneurysmal subarachnoid hemorrhage: a prospective MRI and DSA study. *Stroke* 2007;38:1831-1836.
7. Lysakowski C, Walder B, Costanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: A systematic review. *Stroke* 2001;32:2292-2298.
8. Mir DI, Gupta A, Dunning A, et al. CT perfusion for detection of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *AJNR American journal of neuroradiology* 2014;35:866-871.
9. Dankbaar JW, de Rooij NK, Velthuis BK, Frijns CJ, Rinkel GJ, van der Schaaf IC. Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration. *Stroke* 2009;40:3493-3498.
10. Sloan MA, Haley EC, Jr., Kassell NF, et al. Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology* 1989;39:1514-1518.
11. Hertel F, Walter C, Bettag M, Morsdorf M. Perfusion-weighted magnetic resonance imaging in patients with vasospasm: a useful new tool in the management of patients with subarachnoid hemorrhage. *Neurosurgery* 2005;56:28-35; discussion 35.

ACCEPTED MANUSCRIPT

12. Rordorf G, Koroshetz WJ, Copen WA, et al. Diffusion- and perfusion-weighted imaging in vasospasm after subarachnoid hemorrhage. *Stroke* 1999;30:599-605.
13. Beck J, Raabe A, Lanfermann H, Seifert V, Weidauer S. Tissue at risk concept for endovascular treatment of severe vasospasm after aneurysmal subarachnoid haemorrhage. *Journal of neurology, neurosurgery, and psychiatry* 2004;75:1779-1781.
14. Vajkoczy P, Roth H, Horn P, et al. Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a novel thermal diffusion microprobe. *Journal of neurosurgery* 2000;93:265-274.
15. Meixensberger J, Vath A, Jaeger M, Kunze E, Dings J, Roosen K. Monitoring of brain tissue oxygenation following severe subarachnoid hemorrhage. *Neurological research* 2003;25:445-450.
16. Dings J, Meixensberger J, Jager A, Roosen K. Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. *Neurosurgery* 1998;43:1082-1095.
17. Wilson CD, Shankar JJ. Diagnosing Vasospasm After Subarachnoid Hemorrhage: CTA and CTP. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques* 2014;41:314-319.
18. Greenberg ED, Gold R, Reichman M, et al. Diagnostic accuracy of CT angiography and CT perfusion for cerebral vasospasm: a meta-analysis. *AJNR American journal of neuroradiology* 2010;31:1853-1860.
19. Dankbaar JW, de Rooij NK, Rijsdijk M, et al. Diagnostic threshold values of cerebral perfusion measured with computed tomography for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Stroke* 2010;41:1927-1932.
20. Etminan N, Beseoglu K, Heiroth HJ, Turowski B, Steiger HJ, Hanggi D. Early perfusion computerized tomography imaging as a radiographic surrogate for delayed cerebral ischemia and functional outcome after subarachnoid hemorrhage. *Stroke* 2013;44:1260-1266.
21. Wintermark M, Ko NU, Smith WS, Liu S, Higashida RT, Dillon WP. Vasospasm after subarachnoid hemorrhage: utility of perfusion CT and CT angiography on diagnosis and management. *AJNR American journal of neuroradiology* 2006;27:26-34.
22. Sanelli PC, Jou A, Gold R, et al. Using CT perfusion during the early baseline period in aneurysmal subarachnoid hemorrhage to assess for development of vasospasm. *Neuroradiology* 2011;53:425-434.
23. Dolatowski K, Malinova V, Frolich AM, et al. Volume perfusion CT (VPCT) for the differential diagnosis of patients with suspected cerebral vasospasm: qualitative and quantitative analysis of 3D parameter maps. *European journal of radiology* 2014;83:1881-1889.
24. Othman AE, Afat S, Nikoubashman O, et al. Volume perfusion CT imaging of cerebral vasospasm: diagnostic performance of different perfusion maps. *Neuroradiology* 2016;58:787-792.
25. Hoang JK, Wang C, Frush DP, et al. Estimation of radiation exposure for brain perfusion CT: standard protocol compared with deviations in protocol. *AJR American journal of roentgenology* 2013;201:W730-734.
26. American Association of Physicists in Medicine. Adult brain perfusion CT protocols version 2.0 2016, https://www.aapm.org/pubs/CTProtocols/documents/AdultBrainPerfusionCT.pdf. Accessed May 30, 2017
27. Abels B, Klotz E, Tomandl BF, Kloska SP, Lell MM. Perfusion CT in acute ischemic stroke: a qualitative and quantitative comparison of deconvolution and maximum slope approach. *AJNR American journal of neuroradiology* 2010;31:1690-1698.

ACCEPTED MANUSCRIPT

28. Faust K, Horn P, Schneider UC, Vajkoczy P. Blood pressure changes after aneurysmal subarachnoid hemorrhage and their relationship to cerebral vasospasm and clinical outcome. *Clinical neurology and neurosurgery* 2014;125:36-40.
29. Fontana J, Scharf J, Weiss C, Schmieder K, Barth M. The spontaneous arterial blood pressure rise after aneurysmal subarachnoid hemorrhage - a biphasic phenomenon. *Clinical neurology and neurosurgery* 2015;137:22-27.
30. Waydhas C. Intrahospital transport of critically ill patients. *Critical care* 1999;3:R83-89.
31. Voigt LP, Pastores SM, Raoof ND, Thaler HT, Halpern NA. Review of a large clinical series: intrahospital transport of critically ill patients: outcomes, timing, and patterns. *Journal of intensive care medicine* 2009;24:108-115.
32. Sviri GE, Britz GW, Lewis DH, Newell DW, Zaaroor M, Cohen W. Dynamic perfusion computed tomography in the diagnosis of cerebral vasospasm. *Neurosurgery* 2006;59:319-325; discussion 319-325.
33. Cremers CH, van der Schaaf IC, Wensink E, et al. CT perfusion and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2014;34:200-207.

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Tables:

Table 1. Patient characteristics

Table 2. AUCs with corresponding 95% Cls of optimal CTP threshold values, as well as sensitivities and specificities of the different perfusion maps for the detection of cerebral vasospasm

Figure legends:

Figure 1: Ten ROIs were manually set on two rostro-caudal levels of the acquired CTP: **A)** centrum semiovale and **B)** 3rd ventricle.

Figure 2: CTP parameters of baseline and acute examinations of patients with DCI and controls: **a)** shows MTT, **b)** TTP, **c)** TTD. In patients with DCI, the ROI corresponding to the clinically symptomatic brain area was analyzed (bright grey). The same ROI was selected in the baseline CTP (white). In the clinically unaffected hemisphere the corresponding mirror ROI was selected from the baseline (grey) and acute CTPs (dark grey). In patients without DCI, the ROI placed in the vascular territory of the left MCA at the level of the centrum semiovale was analyzed (bright grey) and compared to the mirror ROI of the right hemisphere (dark grey) and the corresponding ROIs of the baseline CTP respectively (white and grey columns). Columns and whiskers show mean ± SEM; asterisks indicate significant differences by multivariate ANOVA for repeat measures, * = $P < 0.05$, *** = $P < 0.001$

Figure 3: CTP parameters of baseline and acute examinations of patients with DCI and controls: **a)** CBF and **b)** CBV. In patients with DCI, the ROI corresponding to the clinically symptomatic brain area was analyzed (bright grey). The same ROI was selected in the baseline CTP (white). In the clinically unaffected hemisphere the corresponding mirror ROI

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was selected from the baseline (grey) and acute CTPs (dark grey). In patients without DCI, the ROI placed in the vascular territory of the left MCA at the level of the centrum semiovale was analyzed (bright grey) and compared to the mirror ROI of the right hemisphere (dark grey) and the corresponding ROIs of the baseline CTP respectively (white and grey columns). Columns and whiskers show mean ± SEM; asterisks indicate significant differences by multivariate ANOVA for repeat measures, * = $P < 0.05$, *** = $P < 0.001$

Figure 4: Likelihood ratio graphs derived from ROC curves for optimal threshold values: **a)** acute versus baseline CTP, **b)** acute CTP symptomatic hemisphere only and **c)** acute CTP hemispheric comparison. **d)** Diagnostic test qualities. The four regions correlate with overall superiority or overall inferiority of the analyzed modality and their power to show presence or absence of disease.

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Table 1. Patient characteristics

	DCI	No DCI	P-value unpaired *t*-Test
No. of patients	**33**	**23**	
No. of men	**6 (18%)**	**10 (43%)**	
Median age (range)	**53 (36-72)**	**55 (22-80)**	**0.429**
Admission WFNS score			
1	7 (21%)	10 (43%)	
2	9 (27%)	3 (13%)	
3	4 (12%)	3 (13%)	
4	5 (15%)	3 (13%)	
5	8 (24%)	4 (17%)	
BNI score			
1	0 (0%)	0 (0%)	
2	3 (9%)	5 (22%)	
3	15 (45%)	10 (43%)	
4	6 (18%)	6 (26%)	
5	9 (27%)	2 (9%)	
Fisher score			
1	0 (0%)	0 (0%)	
2	1 (3%)	3 (13%)	
3	28 (85%)	18 (78%)	
4	4 (12%)	2 (9%)	
Hunt & Hess score			
1	4 (12%)	8 (35%)	
2	11 (33%)	6 (26%)	
3	7 (21%)	3 (13%)	
4	6 (18%)	4 (17%)	
5	5 (15%)	2 (9%)	
ICB	**12 (36%)**	**7 (30%)**	
Aneurysm location			
ICA	2 (6%)	2 (9%)	
MCA	6 (18%)	2 (9%)	
ACOM	10 (30%)	10 (43%)	
ACA	0 (0%)	1 (4%)	
VA	2 (6%)	0 (0%)	
PICA	1 (3%)	2 (9%)	
SCA	1 (3%)	0 (0%)	
Basilar	2 (6%)	0 (0%)	
A. pericallosa (A2)	1 (3%)	3 (13%)	
PICOM	8 (24%)	3 (13%)	
Aneurysm treatment			
Coiling	24 (73%)	21 (91%)	
Clipping	9 (27%)	2 (9%)	
Median Day of follow up CT after SAH (range)	**9 (5-22)**	**8 (3-13)**	**0.996**

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Table 2. AUCs with corresponding 95% CIs of optimal CTP threshold values, as well as sensitivities and specificities of the different perfusion maps for the detection of cerebral vasospasm

Perfusion map	AUC (95% CI)	Threshold	Sensitivity	Specificity
Absolute values follow-up CTP, symptomatic territory				
MTT (sec)	0.955 (0.909-1.000)	4.15	0.91	0.87
TTP (sec)	0.935 (0.860-1.000)	10.16	0.94	0.87
TTD (sec)	0.992 (0.977-1.000)	4.70	0.97	0.96
cBV (mL/100 g)	0.051 (0.001-0.102)	3.20	0.33	0.13
cBF (mL/100g/min)	0.133 (0.036-0.230)	49.29	0.21	0.13
Interhemispheric comparison follow-up CTP				
MTT difference (sec)	0.955 (0.909-1.000)	0.98	0.67	1.00
TTP difference (sec)	0.996 (0.987-1.000)	0.92	0.91	1.00
TTD difference (sec)	0.992 (0.977-1.000)	0.63	0.97	0.91
cBV ratio (sec)	0.610 (0.463-0.757)	0.96	0.64	0.57
cBF ratio (sec)	0.831 (0.726-0.937)	1.01	0.88	0.65
Comparison follow-up versus baseline CTP				
MTT difference (sec)	0.854 (0.744-0.964)	0.94	0.67	0.96
TTP difference (sec)	0.792 (0.672-0.911)	0.91	0.82	0.65
TTD difference (sec)	0.951 (0.899-1.000)	0.59	0.91	0.87
cBV ratio (sec)	0.656 (0.504-0.808)	1.07	0.67	0.61
cBF ratio (sec)	0.826 (0.720-0.932)	1.04	0.85	0.61

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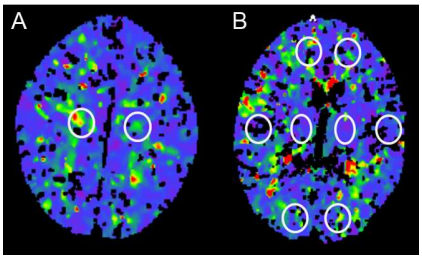

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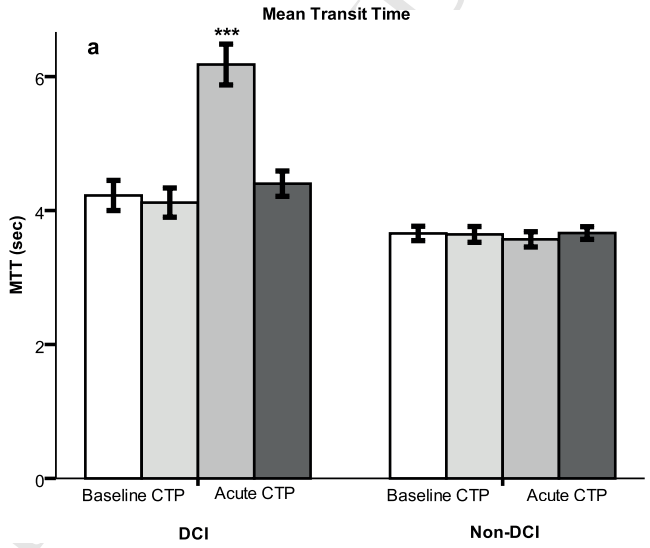

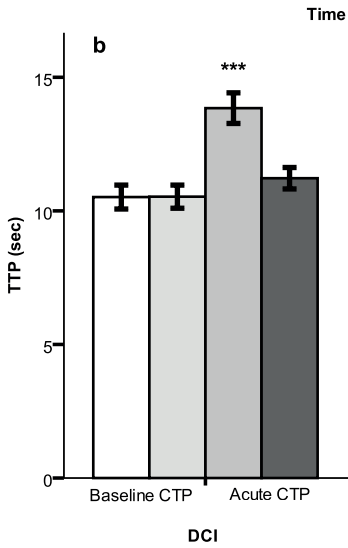

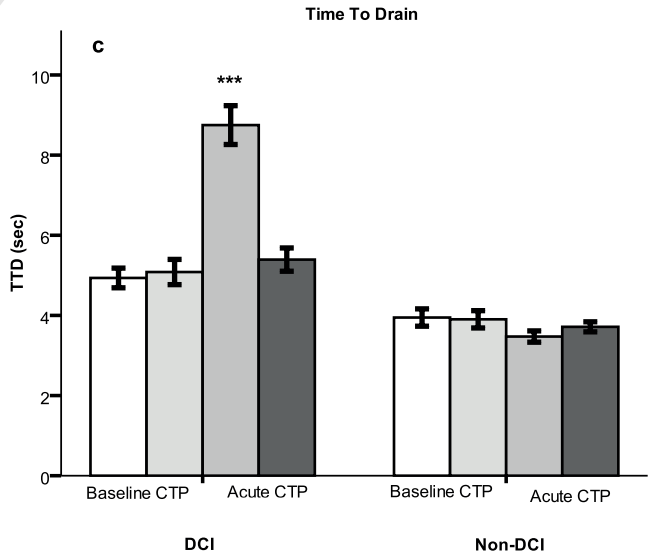

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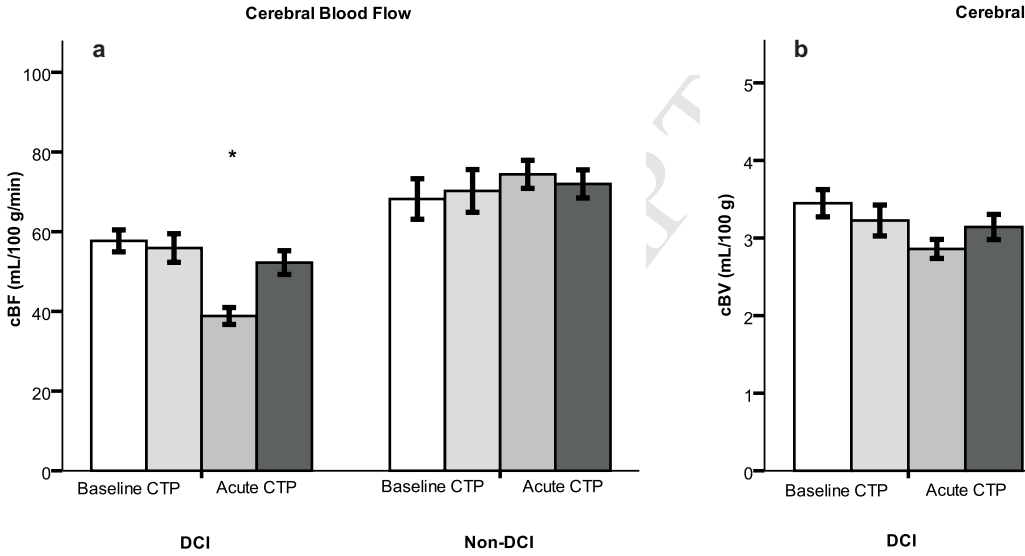

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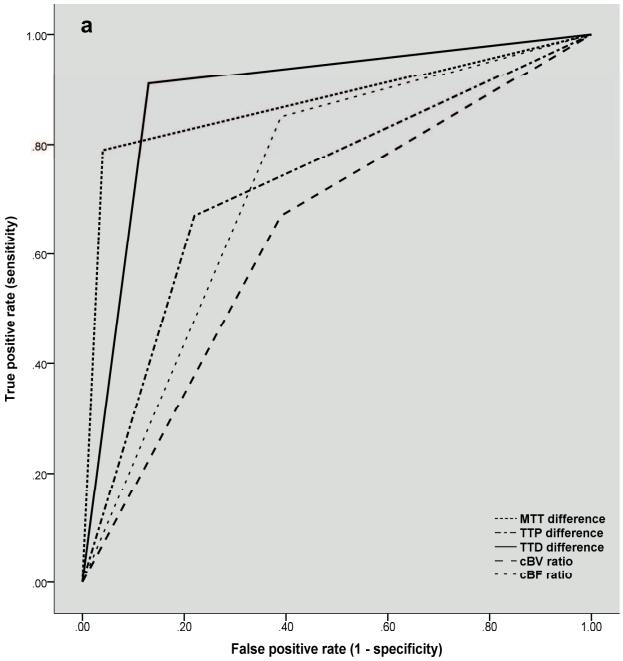
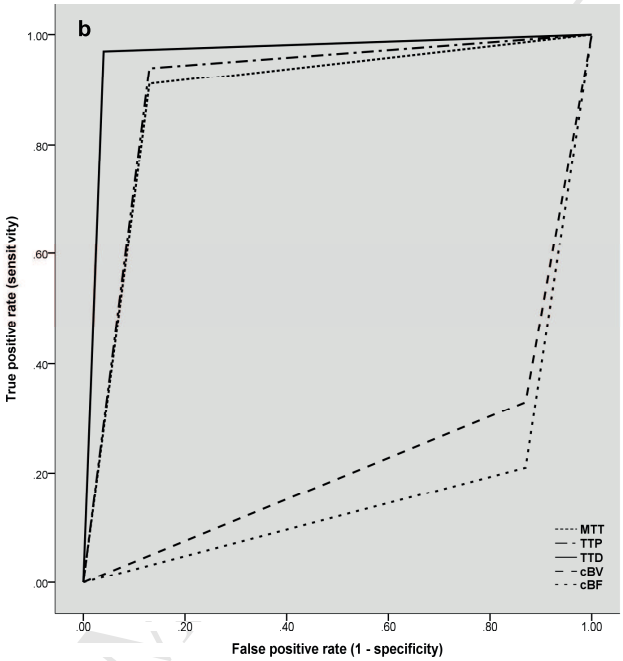
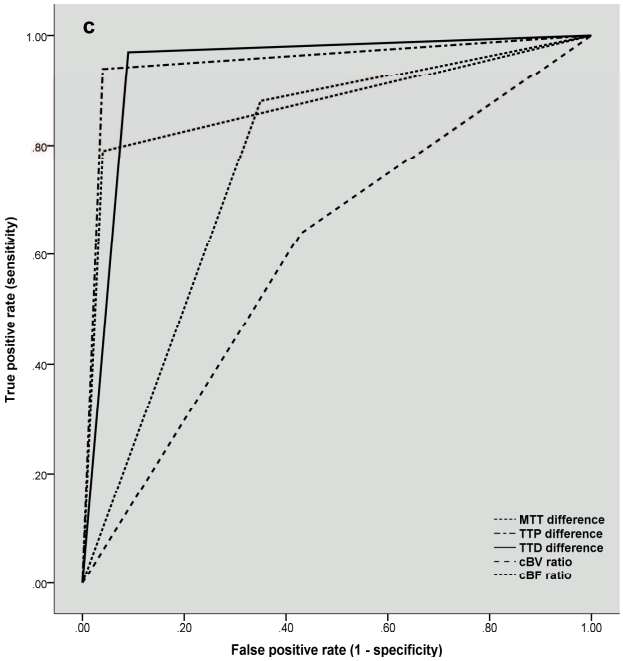

a
True positive rate (sensitivity)
False positive rate (1 - specificity)
MTT difference
TTP difference
TTD difference
cBV ratio
cBF ratio


b
True positive rate (sensitivity)
False positive rate (1 - specificity)
MTT
TTP
TTD
cBV
cBF


c
True positive rate (sensitivity)
False positive rate (1 - specificity)
MTT difference
TTP difference
TTD difference
cBV ratio
cBF ratio

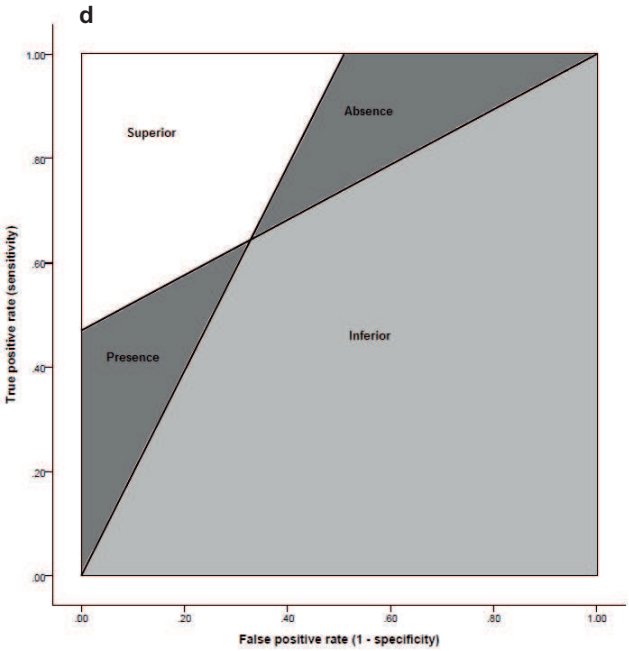

d
True positive rate (sensitivity)
False positive rate (1 - specificity)
Superior
Absence
Presence
Inferior

Figure 4

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Highlights:

- Acute CTP in acute neurological deteriotation due to vasospasm has the highest diagnostic accuracy
- There are no repetitive CTP examinations mandatory
- TTD is the most sensitive parameter to detect critically perfused brain areas
- MTT and TTP are also good reliable parameters to show hypoperfusion

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Dear editor,

All authors have read and approved the submitted manuscript. There is no financial/personal interest or belief that could affect the author's objectivity.

Sonja Vulcu

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