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Dynamic perfusion computerized tomography in cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a comparison with technetium-99m–labeled ethyl cysteinate dimer–single-photon emission computerized tomography

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Object. The aim of this study was to correlate cerebral blood flow (CBF) and mean transient time (MTT) measured on dynamic perfusion computerized tomography (CT) with CBF using ^{99m}Tc ethyl cysteinate dimer–single-photon emission computerized tomography (SPECT) in patients with cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH).

Methods. Thirty-five patients with vasospasm following aneurysmal SAH (12 men and 23 women with a mean age of 49.3 $\pm$ 10.1 years) underwent imaging studies; thus, 35 perfusion CT scans and 35 SPECT images were available for comparison. The CBF and MTT values in 12 different brain regions were defined relative to the interhemispheric occipital cortex values using perfusion CT scans and were compared with qualitative relative (rel)CBF estimated on SPECT images.

In brain regions with normal, mild (relCBF 71–85%), moderate (relCBF 50–70%), and severe (relCBF $<$ 50%) hypoperfusion on SPECT, the mean relCBF values measured on perfusion CT were 1.01 $\pm$ 0.08, 0.82 $\pm$ 0.22, 0.6 $\pm$ 0.15, and 0.32 $\pm$ 0.08, respectively ($p < 0.0001$); the mean relMTT values were 1.04 $\pm$ 0.14, 1.4 $\pm$ 0.31, 2.16 $\pm$ 0.46, and 3.3 $\pm$ 0.54, respectively ($p < 0.0001$). All but one brain region (30 regions) with severe hypoperfusion on SPECT images demonstrated relCBF values less than 0.6 and relMTT values greater than 2.5 on perfusion CT scans.

Conclusions. Relative CBF and MTT values on perfusion CT showed a high concordance rate with estimated relCBF on SPECT in patients with vasospasm following aneurysmal SAH. Given its logistical advantages, perfusion CT may be a valuable method of assessing perfusion abnormality in the acute setting of vasospasm and in patients with an unstable condition following aneurysmal SAH.

Key Words • subarachnoid hemorrhage • vasospasm • cerebral blood flow • computerized tomography • single-photon emission computerized tomography • perfusion computerized tomography

Several perfusion methods are available for assessment of CBF, including xenon-CT, SPECT, PET, and diffusion-weighted and perfusion-weighted MR imaging.[5,6,11,13,14,16,18–21,23,24,29] These methods appear to be sensitive for the detection of vasospasm-related perfusion abnormality. However, none of these methods is ideal given that some are expensive (PET and MR imaging), unavailable on an emergency basis in all or most institutions (PET, MR imaging, and SPECT), or time-consuming (PET, MR imaging, and SPECT); some provide only low-resolution images (xenon-CT) or relCBF measurements (MR imaging and SPECT); and some are generally unsuitable in patients in unstable conditions (SPECT, PET, and MR imaging).

Dynamic perfusion CT is a relatively new imaging technique, which has become widely accepted in the diagnosis of acute stroke.[7,12,26–28] By adding only a few minutes to the duration of a conventional CT study, perfusion CT can be performed using current CT technology and readily available computer software.[7,26] Nonetheless, perfusion CT methods have many limitations related to the deconvolution algorithm[2–4] used for calculation and the assumption of normal cerebral hemodynamic physiological features and an intact blood–brain barrier, which cannot necessarily be assumed after aneurysmal SAH. Furthermore, perfusion val-

Abbreviations used in this paper: ACA = anterior cerebral artery; CBF = cerebral blood flow; CT = computerized tomography; DID = delayed ischemic deterioration; ECD = ethyl cysteinate dimer; HHH = hypertension, hypervolemia, and hemodilution; MCA = middle cerebral artery; MR = magnetic resonance; MTT = mean transient time; PCA = posterior cerebral artery; PET = positron emission tomography; relCBF = relative CBF; relMTT = relative MTT; ROI = region of interest; SAH = subarachnoid hemorrhage; SD = standard deviation; SPECT = single-photon emission CT.

ues are highly dependent on the arterial input function chosen for measurements. Therefore, it is practically impossible to set normal and pathological values of CBF and MTT. To overcome this limitation, perfusion CT measurements of CBF in patients with acute stroke are performed relative to the contralateral side.[27] This solution may not be reliable in vasospasm, however, as the contraction can affect perfusion in multiple vascular territories.

Although the perfusion CT technique has many advantages in the acute setting, it has not been systematically evaluated for the diagnosis of vasospasm-related perfusion abnormalities.[10,17] In the present study we assessed the use of relCBF and relMTT measured on perfusion CT in comparison with the qualitative analysis of CBF obtained on SPECT.

Clinical Material and Methods

Patient Population

The study cohort consisted of 35 patients (12 men and 23 women) with cerebral vasospasm following aneurysmal SAH, all of whom had been treated at Harborview Medical Center between March 2003 and December 2003. The mean patient age was 49.3 ± 10.1 years (mean ± SD) and the range was 35 to 72 years. Aneurysms were located in the anterior circulation in 28 patients and in the posterior circulation in seven. All patients underwent perfusion CT and SPECT within 3 hours of each other (time was calculated between injection of radionuclide and perfusion CT). Thirty-five perfusion CT studies were available for correlation with SPECT images. Studies were obtained between Days 4 and 13 after the initial hemorrhage (median Day 6). In all patients included in the study, severe vasospasm was diagnosed on transcranial Doppler ultrasonography according to criteria proposed by Aaslid, et al.,[1] and Lindegaard, et al.[15] Delayed ischemic deterioration was defined as a worsening in neurological condition that could not be attributed to rebleeding, postoperative complications, hydrocephalus, or systemic complication (interval from perfusion CT scanning 48 hours). Delayed brain infarction was defined by the presence of new hypodense lesions consistent with infarcts on noncontrast-enhanced CT scans obtained 2 to 3 weeks after the initial hemorrhage; these images were compared with a baseline CT scan obtained as part of the perfusion CT study. Aneurysms were secured by craniotomy or coil insertion within 72 hours of bleeding. All patients received HHH therapy that was guided by the use of both central venous and arterial catheters; a mean arterial pressure greater than 100 mm Hg was maintained during the test. Fourteen of the 35 patients were also treated with interventional endovascular therapy.

Dynamic Perfusion CT Studies

Perfusion CT scanning was performed using a multislice helical CT scanner (LightSpeed; GE Medical Systems, Milwaukee, WI). Scanning consisted of an initial noncontrast-enhanced head CT followed by two perfusion CT acquisitions. The perfusion scans were obtained at the centrum semiovale. Four contiguous 5-mm-thick sections were scanned over 55 seconds by using cine techniques. Contrast medium (300 mg/ml Visipaque; Amersham Health, Princeton, NJ) was injected at 4 ml/second for a total dose of 50 ml during scan acquisition. After scanning, data were transferred to a workstation and analyzed using commercial perfusion CT software (CT PERFUSION II; GE Medical Systems). In most patients, the larger of the two ACAs was chosen as the ROI providing the arterial input function, and the superior sagittal sinus was chosen as the ROI providing the venous outflow function. These vessels were chosen because they are reliably identified in most patients and because their courses run nearly perpendicular to the transverse plane of section used in CT scanning of the brain (assuming that by choosing these perpendicularly oriented vessels, errors due to volume-averaging artifacts would be decreased).

Parametric maps of CBF and MTT were calculated by applying the deconvolution algorithm and were evaluated using the ROI in the cortical area of the specific brain region (anterofrontal, parasagittal, posterofrontal, parietal, posterotemporal, and basal ganglia regions).[28] Multiple ROI measurements (circular, 1.5–2 cm) were used to cover the cortex and basal ganglia regions. Both CBF and MTT were then evaluated relative to their values in the interhemispheric occipital cortex, which is supplied exclusively by the PCAs.[25] During calculations, the average interhemispheric occipital cortex values of both sides were used unless asymmetry was noticed, and then measurements were taken from the side with the better perfusion map. If values of the interhemispheric occipital cortex regions were 15% lower than those in other brain regions, the scan was excluded (Fig. 1). Using these exclusion criteria, 72 (86.7%) of 83 perfusion CT scans obtained for the diagnosis of vasospasm at our institution during the study period were adequate for this method of relCBF and relMTT measurements. If perfusion was impaired in the watershed area (for example, between the anterior and posterior frontal regions, which represents the watershed between the ACA and MCA; or between posterior temporal and occipital regions, which represents the watershed area between the MCA and PCA), the values were added to the adjacent region having the most impaired perfusion. Two independent observers, who were blinded to the patients' SPECT findings, performed the measurements.

Single-Photon Emission Computerized Tomography Studies

The ^{99m}Tc ECD-SPECT imaging technique and data acquisition methods and interpretation have been reported previously.[22] For analytical and descriptive purposes, hypoperfusion was defined as mild (71–85% of baseline uptake on SPECT images), moderate (50–70% of baseline uptake), or severe (< 50% of baseline uptake); this grading system is currently used in our clinical practice.[8,9,14,20,22] All patients underwent baseline ^{99m}Tc ECD-SPECT imaging within 72 hours of the initial hemorrhage. Two nuclear medicine physicians analyzed all SPECT images by consensus reading.

Statistical Analysis

For all data presented as the means ± SDs, the various subgroups were compared using an analysis of variance and alternate t-test. Differences were considered significant when they reached a probability value less than 0.05.

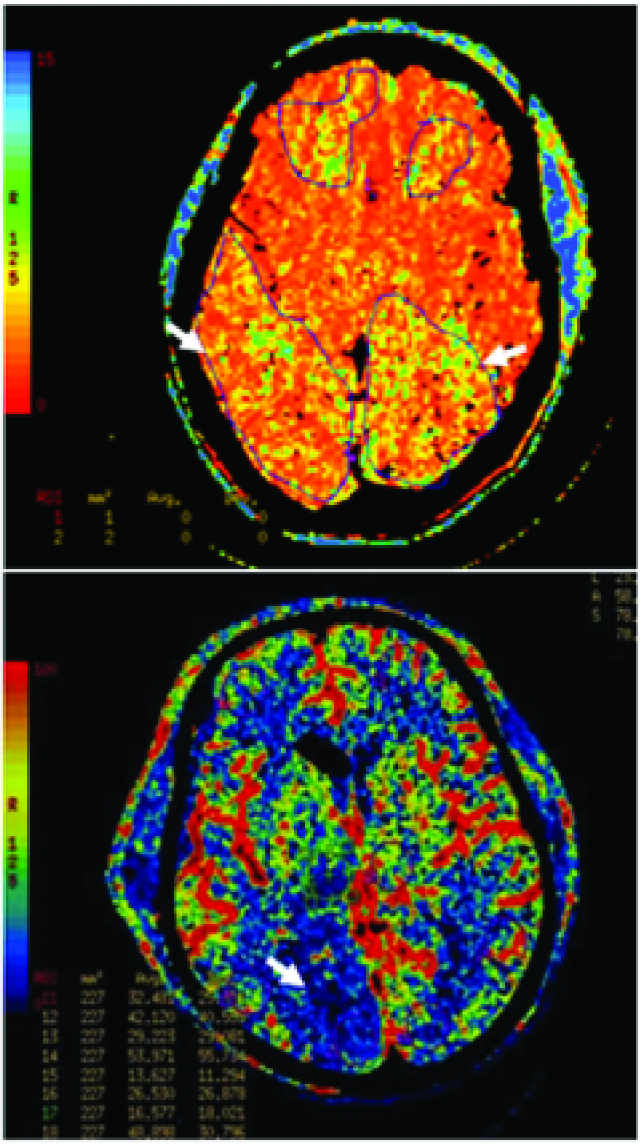

FIG. 1. Perfusion CT scans demonstrating MTT and CBF maps in two different patients with vasospasm following aneurysmal SAH, in whom images for relative measurements of MTT and CBF in comparison with the interhemispheric occipital cortex could not be obtained because the reference area was impaired. *Upper:* Map *(arrows)* of elevated MTT values in bilateral PCA territories (scale ranging 0–15 seconds, regions with elevated MTT are marked by *black line*). *Lower:* Cerebral blood flow in the occipital regions *(arrow)* is severely impaired compared with the rest of the brain (scale ranging 0–100 ml/100 g/min).

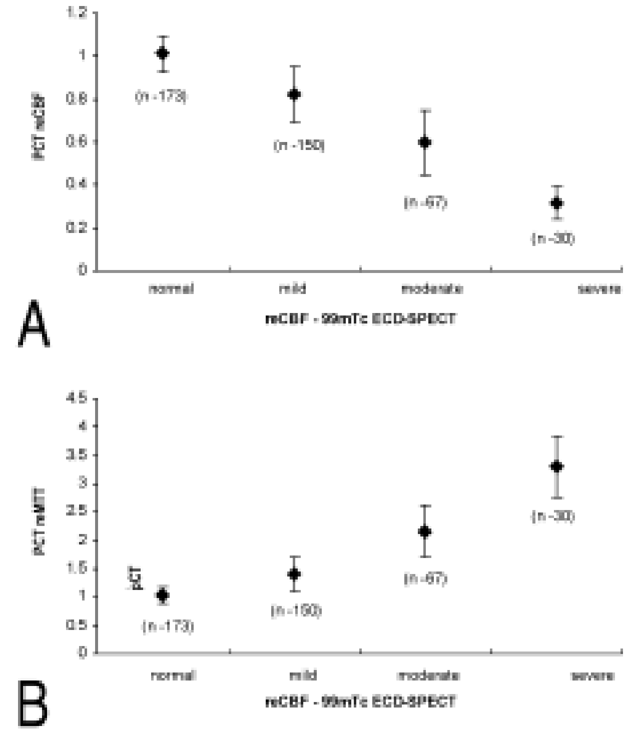

FIG. 2. Graphs depicting relCBF (A) and relMTT (B) measured on perfusion CT (PCT) in 35 patients with vasospasm following aneurysmal SAH. Data are presented as the means ± SD in 420 brain regions compared with qualitative relCBF measured on ^{99m}Tc ECD-SPECT ($p < 0.0001$ for differences between the values). Mild, moderate, and severe represent mild, moderate, and severe ischemia. n = number of regions measured; reCBF = relCBF; reMTT = relMTT.

Results

Thirty-five perfusion CT scans and 35 ^{99m}Tc ECD-SPECT images were available for comparison. Indications for perfusion scanning consisted of neurological deterioration in 19 cases and worsening of transcranial Doppler ultrasonography measurements showing severe vasospasm without neurological deterioration in 16 cases. Both relCBF and relMTT values measured in the different areas on perfusion CT scans correlated with the severity of hypoperfusion estimated using ^{99m}Tc ECD-SPECT studies (Table 1). The relCBF values in areas measured on perfusion CT scans and for which ^{99m}Tc ECD-SPECT had disclosed severe hypoperfusion were significantly lower than the values in areas for which ^{99m}Tc ECD-SPECT had disclosed moderate or mild hypoperfusion or normal perfusion (1.01 ± 0.08, 0.82 ± 0.22, 0.6 ± 0.15, and 0.32 ± 0.08, respectively; $p < 0.0001$; Fig. 2). The relMTT values in areas measured on perfusion CT scans and for which ^{99m}Tc ECD-SPECT had disclosed severe hypoperfusion were significantly higher than the values in areas for which ^{99m}Tc ECD-SPECT had disclosed moderate or mild hypoperfusion or normal perfusion (1.04 ± 0.14, 1.4 ± 0.31, 2.16 ± 0.46, and 3.3 ± 0.54, respectively; $p < 0.0001$).

All but one region (30 regions) with severe hypoperfusion on ^{99m}Tc ECD-SPECT images demonstrated an relCBF less than 0.6 and an relMTT greater than 2.5 on perfusion CT scans. Fifty-four (80%) of 67 areas with moderate hypoperfusion according to SPECT exhibited relCBF values less than 0.75 on perfusion CT; 49 (73%) of 67 had relMTT values greater than 1.75 on perfusion CT. In only 35 (10.8%) of 323 areas for which ^{99m}Tc ECD-SPECT had shown mild hypoperfusion or normal perfusion were relCBF values less than 0.75 on perfusion CT; in only 21 areas (6.5%) were relMTT values greater than 1.75 on perfusion CT. Illustrative cases are presented in Figs. 3, 4, and 5.

On perfusion CT scans, the relCBF values in brain regions (41 regions) that eventually developed infarcts were

TABLE 1
*Comparison of findings on perfusion CT and ^{99m}Tc ECD-SPECT**

Perfusion CT Indicators	Perfusion State on ^{99m}Tc ECD-SPECT Imaging (no. of regions measured)			
	Normal	Mild Hypoperfusion	Mod Hypoperfusion	Severe Hypoperfusion
parasagittal				
relCBF	0.97 ± 0.08 (28)	0.88 ± 0.16 (23)†	0.65 ± 0.19 (10)‡	0.32 ± 0.06 (9)‡
relMTT	1.04 ± 0.15 (28)	1.38 ± 0.29 (23)‡	1.89 ± 0.2 (10)‡	3.39 ± 0.58 (9)‡
anterofrontal				
relCBF	1.03 ± 0.07 (37)	0.84 ± 0.16 (19)‡	0.61 ± 0.25 (8)§	0.33 ± 0.11 (6)‡
relMTT	0.98 ± 0.07 (37)	1.45 ± 0.37 (19)‡	2.28 ± 0.41 (8)‡	2.88 ± 0.199 (6)§
posterofrontal				
relCBF	0.99 ± 0.04 (23)	0.79 ± 0.13 (28)‡	0.6 ± 0.13 (14)‡	0.29 ± 0.02 (5)‡
relMTT	0.98 ± 0.07 (23)	1.51 ± 0.4 (28)‡	2.3 ± 0.43 (14)‡	2.9 ± 0.22 (5)§
parietal				
relCBF	1.01 ± 0.79 (27)	0.84 ± 0.11 (30)‖	0.53 ± 0.16 (10)‡	0.32 ± 0.08 (3)‖
relMTT	1.04 ± 0.11 (27)	1.39 ± 0.37 (30)‡	2.34 ± 0.45 (10)‡	3.07 ± 0.87 (3)‖
posterotemporal				
relCBF	1.04 ± 0.08 (30)	0.81 ± 0.07 (17)‡	0.59 ± 0.11 (16)‡	0.34 ± 0.09 (7)‡
relMTT	1.06 ± 0.14 (30)	1.35 ± 0.21 (17)‡	2.37 ± 0.47 (16)‡	3.36 ± 0.36 (7)‡
basal ganglia				
relCBF	1.1 ± 0.2 (28)	0.8 ± 0.11 (33)‡	0.5 ± 0.27 (9)‡	(0)
relMTT	1.04 ± 0.08 (28)	1.37 ± 0.25 (33)‡	1.86 ± 0.2 (9)‡	(0)

* Values are presented as the means ± SDs and represent ratios obtained using perfusion CT. Abbreviation: mod = moderate.
† $p < 0.05$, compared with values for normal perfusion.
‡ $p < 0.001$, compared with values for normal perfusion.
§ $p < 0.01$, compared with values for normal perfusion.
‖ Not significant.

significantly lower than values in regions that did not develop infarcts (0.59 ± 0.26 compared with 0.86 ± 0.21, respectively; $p < 0.0001$). In contrast, the relMTT values in these same 41 regions that eventually developed infarcts were significantly higher than the relMTT values in regions that did not develop infarcts (2.36 ± 1.01 compared with 1.41 ± 0.58, respectively; $p < 0.0001$). The minimal relCBF values in patients with DID (19 patients) were significantly lower than the minimal relCBF values in patients without DID (16 patients; 0.35 ± 0.11 compared with 0.72 ± 0.31, respectively; $p = 0.0003$). The maximal relMTT values in patients with DID (19 patients) were significantly higher than the maximal values in patients without DID (16 patients; 3.3 ± 0.58 compared with 1.75 ± 0.61, respectively; $p < 0.0003$).

Discussion

In the present study we evaluated the correlation between qualitative relCBF estimated on ^{99m}Tc ECD-SPECT imaging and relCBF and relMTT measurements on perfusion CT scanning in patients with vasospasm after aneurysmal SAH. Although SPECT provides only a relative and qualitative estimation of the CBF, various authors have found it to be a reliable means of measuring CBF in the context of vasospasm.[2,6,11,14,19–21,24] At our institution, SPECT imaging has been used in the diagnosis of vasospasm for more than 14 years. In performing more than 600 ^{99m}Tc ECD-SPECT studies every year for this indication, we,[8,9,14,22,29] like other authors,[6,11,19,21,24] have found the procedure to be a very reliable imaging modality for the assessment of vasospasm-related perfusion impairments, and thus it has been established at our institution as a standard of care for this purpose. To increase SPECT accuracy, all patients included in the present study underwent baseline studies within 72 hours of the initial hemorrhage, usually on the 1st postoperative day or the 1st day after coil embolization.

The relCBF and relMTT in the different brain regions on perfusion CT scans were measured in comparison with values in the interhemispheric occipital cortex, which is exclusively supplied by the PCAs.[25] Using this method, we found a high concordance rate between estimated relCBF on SPECT imaging and the relCBF and relMTT values on perfusion CT scanning. Almost all patients with severe hypoperfusion on SPECT images showed significantly reduced relCBF on perfusion CT studies, and the relCBF and relMTT values were found to correlate with the patients' clinical courses. Furthermore, most regions with unimpaired perfusion or mildly impaired relCBF on SPECT images appeared unimpaired or only mildly impaired on perfusion CT scans. Nevertheless, it is necessary to mention that our findings represent measurements in patients with vasospasm treated with HHH therapy and do not necessarily show the variability of relative perfusion abnormalities in all patients with aneurysmal SAH, particularly those in whom HHH therapy was not administered. Furthermore, although the PCAs are less involved in vasospasm than the anterior circulation arteries, we must consider that perfusion impairments in these territories may further bias the results. Due to current limitations in software, perfusion CT measurements can only be achieved by multiple circular ROI computations. At present, there is no possibility for template measurements, and this shortcoming can lead to biased results. Additionally, to evaluate more precisely the perfusion status, the radionuclide material should be injected at the time of perfusion CT scanning. In the present study SPECT and perfusion CT imaging were performed in temporal proximity; given the dynamic nature of vasospasm, there could be bias related to any time discrepancy. Furthermore,

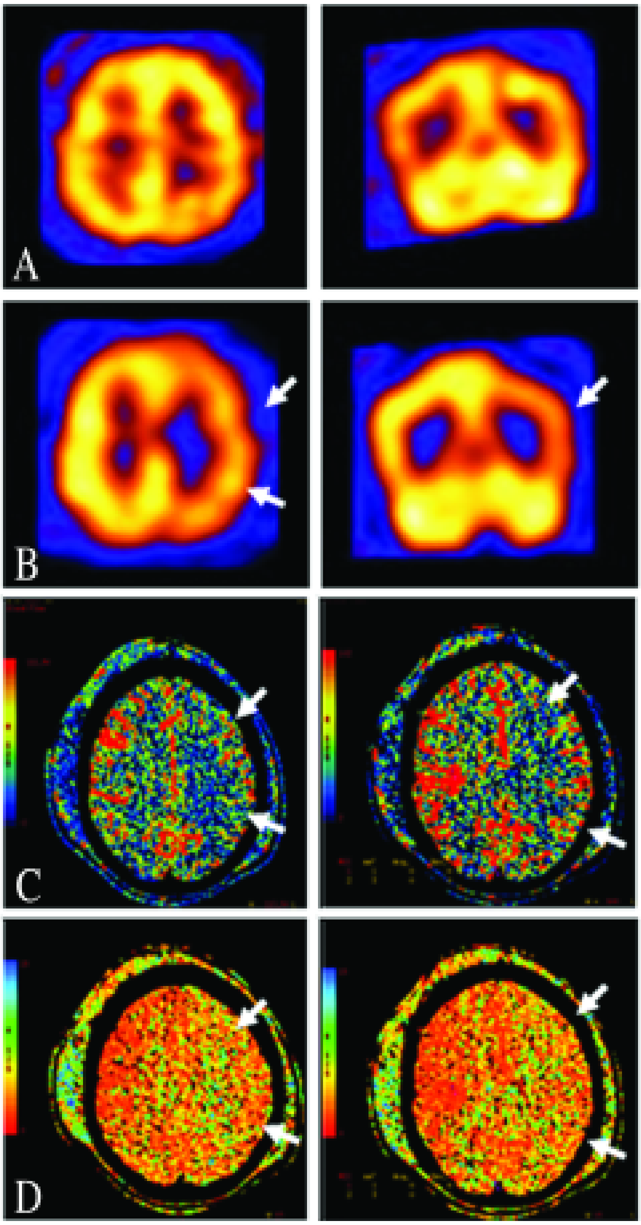

FIG. 3. Baseline ^{99m}Tc ECD-SPECT images (A) obtained in a 41-year-old man, revealing SAH caused by the rupture of a right MCA aneurysm. On Day 6 after the initial hemorrhage, he suffered right hemiparesis. Single-photon emission CT images (B) showing moderately decreased perfusion in the left posterior frontal and parietal regions *(white arrows)*, indicating a left MCA vasospasm. Perfusion CT scans showing reduced relCBF (C) and elevated relMTT (D) in the corresponding regions *(white arrows)*. Scales range between 0 and 100 ml/100 g/min for the CBF map and between 0 and 15 seconds for the MTT map.

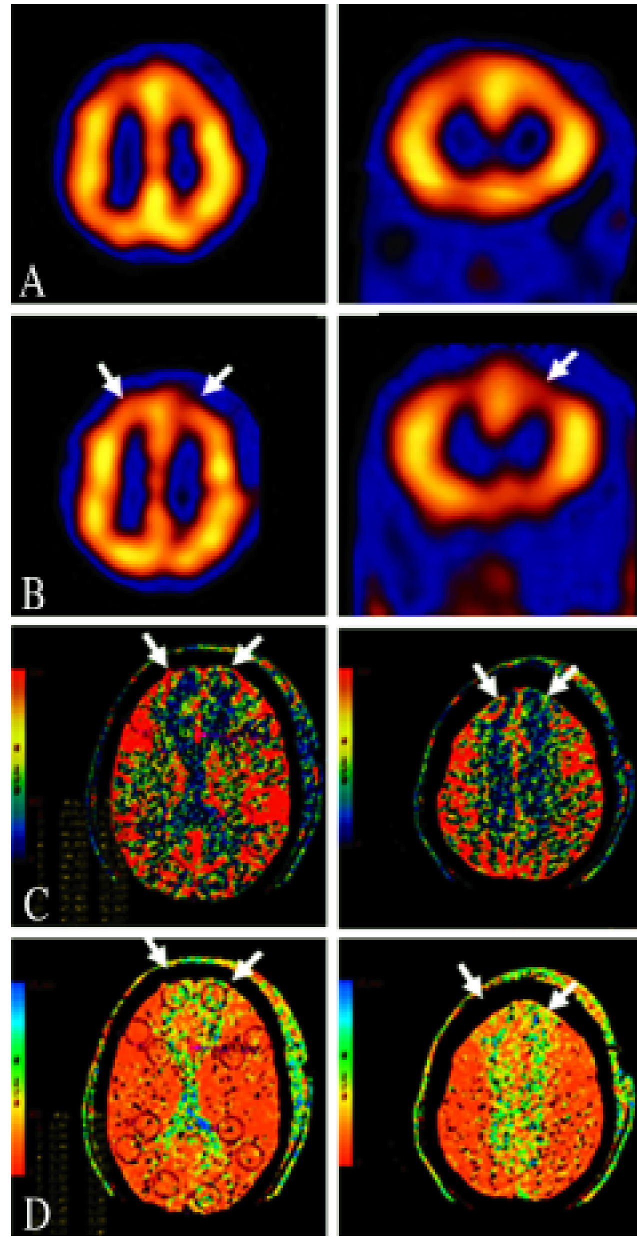

FIG. 4. Baseline ^{99m}Tc ECD-SPECT images (A) obtained in a 29-year-old woman, demonstrating an SAH caused by the rupture of an anterior communicating artery aneurysm. On Day 4 after the initial hemorrhage, she became drowsy. Single-photon emission CT images (B) showing moderately decreased perfusion in the bilateral anterior frontal and parasagittal regions *(white arrows)*, indicating bilateral ACA vasospasm. Perfusion CT scans showing reduced relCBF (C) and elevated relMTT (D) in the corresponding regions *(white arrows)*. Scales range between 0 and 100 ml/100 g/min for the CBF map and between 0 and 15 seconds for the MTT map.

perfusion evaluation using perfusion CT is limited to selected brain areas visualized in chosen axial slices (unlike global SPECT), does not provide information in all brain regions (for example, thalamic nuclei, brainstem, and cerebellum), and is inaccurate around metal structures such as dental implants and aneurysm clips.

Nevertheless, perfusion CT has major advantages over other perfusion methods in the acute setting of vasospasm when rapid treatment decisions are necessary.[20] It can be performed immediately after conventional CT scanning and is highly suitable for the evaluation of unstable or uncooperative patients. More importantly, because a helical CT scanner with the appropriate software is all that is needed for assessment, perfusion CT can be a practical solution for many

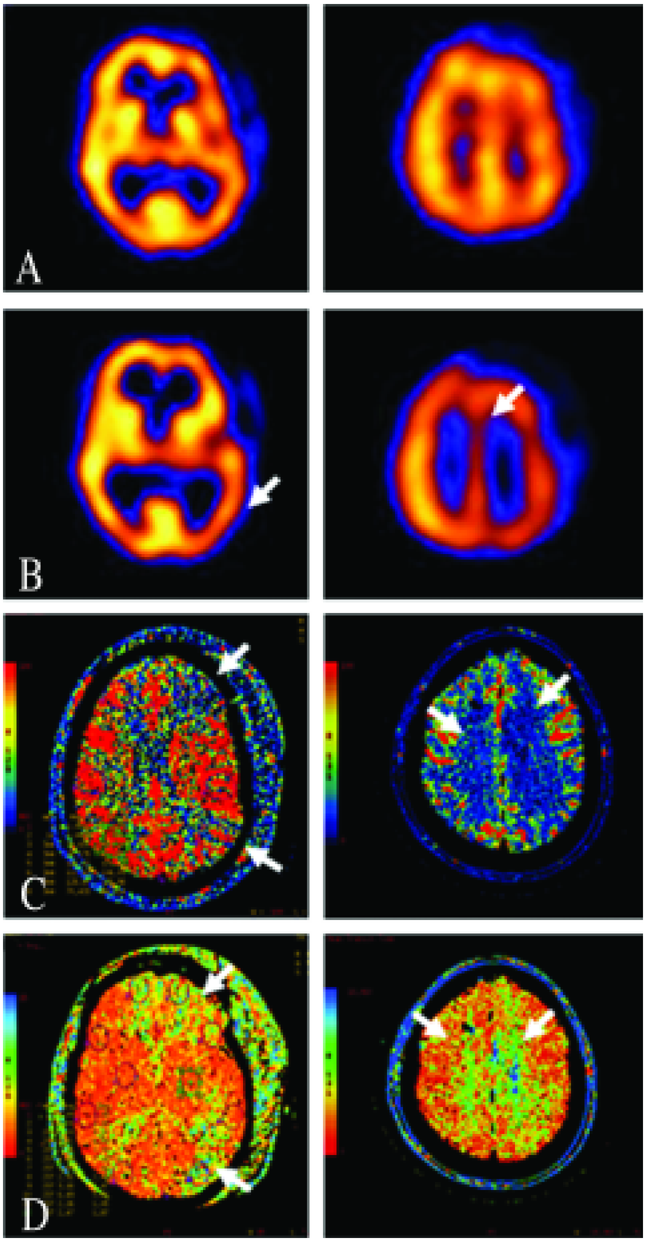

FIG. 5. Baseline ^{99m}Tc ECD-SPECT images (A) obtained in a 49-year-old man, exhibiting SAH caused by the rupture of an anterior communicating artery aneurysm. On Day 7 after the initial hemorrhage, he experienced right hemiparesis and became somnolent. Single-photon emission CT images (B) showing moderately to severely decreased perfusion in the bilateral parasagittal, left anterior and posterior frontal, and left temporal and occipital regions *(white arrows)*, representing bilateral ACA and left MCA vasospasm. Perfusion CT scans showing reduced relCBF (C) and elevated relMTT (D) in the corresponding regions *(white arrows)*. Scales range between 0 and 100 ml/100 g/min for the CBF map and between 0 and 15 seconds for the MTT map.

institutions with limited financial resources. Current improvements in the software allow easier data acquisition in the context of vasospasm. Nevertheless, given the involvement of multiple vascular territories, interpretation of perfusion CT maps for vasospasm may be more complex than those for acute stroke. Close cooperation among neurosurgeons, intensive care teams, and radiologists as well as clear communication about neurological findings, hemodynamic issues, and ongoing treatments is essential to provide better interpretation of the perfusion CT study.

Conclusions

Relative analysis of perfusion CT maps comparing CBF and MTT in various brain regions with those in the interhemispheric occipital cortex shows a high correlation with estimated relCBF on SPECT imaging in patients with altered perfusion due to vasospasm. The value of the perfusion CT scanning technique in vasospasm and its role in comparison with other methods requires further evaluation.

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