Clinical application of perfusion computed tomography in neurosurgery

Clinical article

ABEL PO-HAO HUANG, M.D.,1,2,4 JU-I CHANG TSAI, M.D., PH.D.,1,3 LU-TING KUO, M.D., PH.D.,1,2,4 CHUNG-WEI LEE, M.D.,1 HONG-SHIEE LAI, M.D., PH.D.,2 LI-KAI TSAI, M.D.,1 SHENG-JEAN HUANG, M.D.,1,4 CHEN-MIN CHEN, M.D.,5 YUAN-SHEN CHEN, M.D.,1,2,4 HAO-YU CHUANG, M.D.,6 AND MAX WINTERMARK, M.D., M.A.S.7

1Division of Neurosurgery, 2Department of Surgery, National Taiwan University Hospital, Taipei; 3Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei; 4Division of Neurosurgery, Department of Surgery, National Taiwan University Hospital, Yun-Lin branch, Yun-Lin; 5Department of Neurosurgery, Chang-Hau Christian Hospital, Chang-Ha; 6Department of Neurosurgery, China Medical University, Bei-Gang Hospital, Yun-Lin, Taiwan; and 7Neuroradiology Division, Department of Radiology, University of Virginia, Charlottesville, Virginia

Object. Currently, perfusion CT (PCT) is a valuable imaging technique that has been successfully applied to the clinical management of patients with ischemic stroke and aneurysmal subarachnoid hemorrhage (SAH). However, recent literature and the authors’ experience have shown that PCT has many more important clinical applications in a variety of neurosurgical conditions. Therefore, the authors share their experiences of its application in various diseases of the cerebrovascular, neurotraumatology, and neurooncology fields and review the pertinent literature regarding expanding PCT applications for neurosurgical conditions, including pitfalls and future developments.

Methods. A pertinent literature search was conducted of English-language articles describing original research, case series, and case reports from 1990 to 2011 involving PCT and with relevance and applicability to neurosurgical disorders.

Results. In the cerebrovascular field, PCT is already in use as a diagnostic tool for patients suspected of having an ischemic stroke. Perfusion CT can be used to identify and define the extent of the infarct core and ischemic penumbra core, and thus aid patient selection for acute reperfusion therapy. For patients with aneurysmal SAH, PCT provides assessment of early brain injury, cerebral ischemia, and infarction, in addition to vasospasm. It may also be used to aid case selection for aggressive treatment of patients with poor SAH grade. In terms of oncological applications, PCT can be used as an imaging biomarker to assess angiogenesis and response to antiangiogenetic treatments, to differentiate between glioma grades, and to distinguish recurrent tumor from radiation necrosis. In the setting of traumatic brain injury, PCT can detect and delineate contusions at an early stage. In patients with mild head injury, PCT results have been shown to correlate with the severity and duration of postconcussion syndrome. In patients with moderate or severe head injury, PCT results have been shown to correlate with patients’ functional outcome.

Conclusions. Perfusion CT provides quantitative and qualitative data that can add diagnostic and prognostic value in a number of neurosurgical disorders, and also help with clinical decision making. With emerging new technical developments in PCT, such as characterization of blood-brain barrier permeability and whole-brain PCT, this technique is expected to provide more and more insight into the pathophysiology of many neurosurgical conditions.

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Key Words • aneurysmal subarachnoid hemorrhage • perfusion CT • blood-brain barrier
neurosurgical conditions. In this article, we first present a general description of PCT technique and interpretation of its results, and we share our experience in terms of PCT application to cerebrovascular diseases, traumatic brain injury (TBI), and neurooncology.

Methods

In addition to presenting data from our patients who benefited from PCT, we also review the pertinent literature regarding the expanding applications of PCT. Our literature search included English-language articles describing original research, case series, and case reports from 1990 to 2011 involving PCT and with relevance and applicability to neurosurgical disorders. This study is not comprehensive; it is intended to depict the major uses of PCT to date rather than all uses. It is also important to recognize that most of the references cited are of Level C recommendations, or of Level 4 (case series) and Level 5 (expert opinion) evidence, according to the Oxford Centre for Evidence-based Medicine. Therefore, some conclusions may reflect the bias of the authors. The study protocol was approved by the National Taiwan University Hospital review board, Taipei, Taiwan, and each patient from our institution provided written, informed consent.

The General Concept of PCT and the Assessment of Cerebral Vascular Autoregulation

Perfusion CT consists of acquiring sequential CT images during the wash-in and washout of an iodinated contrast agent through the brain tissue. From this data, time-enhancement curves are created in each voxel of the images, and postprocessing software analyzes these curves to create parametric maps of cerebral perfusion. Currently most postprocessing software is completely automated. Cerebral perfusion can be described in terms of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT or time to peak).

From these basic maps, the status of the cerebral vascular autoregulation can be inferred. Mean transit time is the most sensitive parameter and will show abnormally increased values in the vast majority of pathological conditions affecting the cerebral perfusion. While cerebral autoregulation is preserved, cerebral arterioles will still have the ability to dilate in response to a triggering ischemic stimulus (the MTT increase), and the CBV will increase. If cerebral autoregulation is lost, CBV will decrease.

Advanced PCT analysis can extract information about the permeability of the blood-brain barrier (BBB) from time-enhancement curves, for instance using the Patlak model. Microvascular permeability is a metric of BBB integrity and is calculated by measuring the leakage of an intravascular tracer into the extravascular (interstitial) space. We describe below how the PCT technique can be used to enhance diagnosis and guide treatment of patients with cerebrovascular conditions (including stroke, moyamoya disease, and vasospasm), TBI, and brain tumors.

Cerebrovascular Implications of PCT

Acute Ischemic Stroke

Stroke remains a very important cause of death in many countries and is therefore an important focus of clinical research. Recent progress in both diagnostic and therapeutic techniques has led to substantial modification in the clinical management of these patients. Noncontrast head CT remains the first choice in terms of imaging in patients with suspected stroke because it can exclude intracranial hemorrhage (ICH) and is easier and faster to obtain compared with MRI. It is also used to exclude patients with large cerebral infarction from reperfusion therapies, because of the significantly increased risk of hemorrhagic complications in these patients.

With the development of PCT and CT angiography (CTA) technology, the presence of vascular occlusion, the degree and extent of cerebral ischemia, and collaterals can now be identified or even quantitated in these patients. Through its ability to assess the preservation or loss of cerebral vascular autoregulation, PCT in the setting of stroke can differentiate between the infarct core (lost autoregulation) and the ischemic penumbra (preserved autoregulation). PCT provides quantitative information about the extent of the tissue at risk that may be salvageable by the administration of early reperfusion therapy.

An irreversible infarct core will not benefit from reperfusion and may indicate an increased risk of hemorrhage after treatment. Recently, this information has been used to select patients beyond the conventional time window or patients with wake-up strokes for reperfusion therapy. A growing number of clinical trials also use PCT for patient selection. As an illustration, patients with PCT demonstrating more than one-third at-risk territory with nonsalvageable brain (low CBV) are excluded from reperfusion in the Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial.

Progressive neurological and mental status deterioration due to massive cerebral edema occurs in 10%–15% of stroke patients, and the term “malignant infarction” has been used to describe this complication. Perfusion CT, through its assessment of BBB permeability, has been shown as able to predict which patients are at increased risk for malignant infarction. It remains to be clarified if an abnormally increased BBB permeability on PCT is an indicator for early decompressive craniectomy to improve patients’ outcomes. Dittrich et al. have also reported that if the volume of the infarct core is larger than 100 cm³, it is likely to increase the risk of malignant infarction that might require prompt craniectomy. These data are compatible with the data of Oppenheim et al., who used the volume of the diffusion-weighted MRI abnormality to predict massive brain edema.

Hemorrhagic transformation after thrombolytic therapy in patients with ischemic stroke is a devastating complication, occurring in approximately 5% of patients. The exact pathogenesis is still debated, although cerebral ischemia and reperfusion leading to BBB disruption are two important causes of blood extravasation in these patients. Using PCT to assess BBB permeability, Lin et al.
showed that an abnormally elevated BBB permeability is predictive of hemorrhagic transformation in patients who received tissue plasminogen activator. Aviv et al. demonstrated that an elevated BBB permeability is highly sensitive and specific for future hemorrhagic transformation. Figure 1 depicts a case of ischemic stroke and elevated BBB permeability with subsequent hemorrhagic transformation.

In conclusion, PCT can be used not only for the diagnosis of ischemic stroke but also for the prediction of complications after stroke, such as malignant brain edema and hemorrhagic transformation, and for the selection of patients for reperfusion therapies. Patients at high risk for clinical deterioration may be candidates for decompressive craniectomy.

Chronic Cerebral Ischemia

In patients with carotid stenosis, PCT can help in determining the hemodynamic significance of the stenosis. Cerebral blood flow is usually preserved, at least initially, because of the cerebrovascular reserve (CVR). The CVR is a compensating mechanism, which involves the ability of cerebral arteries to dilate to compensate for a trend of CBF to decrease and maintain CBF at its normal level. Brain tissue that has exhausted its vasodilatation ability and has no residual CVR is at higher risk of ischemia, which can be triggered by even minor hemodynamic stress. This requires intervention to increase CBF, usually through carotid stenting or carotid endarterectomy, or surgical revascularization. Therefore, in patients with chronic cerebral vascular disorders, it is important to quantify CVR. Cerebrovascular reserve can be used to assess the stage of hemodynamic compromise, and it has been shown that patients with Stage III hemodynamic compromise are most likely to respond to surgical revascularization. Many other studies that assess the CVR via different imaging tools also support this concept. The CVR concept has also been used in revascularized patients to predict long-term outcome. In summary, CVR may be informative of prognosis and patient selection, evaluating the effect of surgery, and predicting the outcome after surgery.

Hemodynamic stress can be mimicked by a tolerance test such as an acetazolamide challenge, which consists of the administration of acetazolamide in conjunction with quantitative measurement of CBF. Acetazolamide causes vasodilatation of normal cerebral arteries and an increase in CBF in the corresponding territory. In patients with impaired CVR, however, the vessels are already maximally dilated due to the response of cerebral autoregulatory mechanisms, and thus arteries in affected territories cannot respond further to acetazolamide. Therefore, CBF does not increase after acetazolamide challenge and may remain stable or even decrease, as a result of a steal phenomenon by the “healthy” arteries. Some reports suggest that PCT, through its assessment of not only CBF but also MTT and CBV, can obviate the need for an acetazolamide challenge.

**Fig. 1.** Axial images from a patient with acute ischemic stroke who underwent PCT on admission, showing prolonged MTT (A) and reduced CBF (B) in the right MCA territory, with reduced CBV (C) in the region of the right insula. This pattern is consistent with an infarct core (red) in the region of the right insula, and penumbra (green) in the remainder of the right MCA territory (D). Blood-brain barrier permeability evaluation from the PCT data (E) revealed an area of abnormally increased permeability within the infarcted area. This area constituted the epicenter of a large hemorrhagic transformation of the ischemic stroke, as noted on the CT scan (F). PS = permeability surface.
Moyamoya Disease

Perfusion CT is of clinical use not only in patients with acute ischemic stroke and in patients with carotid stenosis and chronic ischemia, but also in patients with less frequent conditions such as moyamoya disease. Moyamoya disease is characterized by progressive steno-occlusive changes in the distal internal carotid arteries (ICAs) and the development of a fine vascular collateral network in the basal ganglion, the so-called “moyamoya” vessels. The leptomeningeal collaterals from the posterior cerebral artery and the transdural collaterals from the external carotid artery are also important collateral pathways to compensate for the diminished ICA flow. The clinical course in these patients is difficult to predict with angiography alone. Therefore, recent studies have used different perfusion and metabolic imaging methods in attempts to gain a better understanding of the course of this peculiar disease.2 The clinical use of PCT in moyamoya disease has been reported. Although baseline PCT parameters are not reliable for predicting impaired CVR in moyamoya patients, an important parameter that has been shown to correlate with the risk of subsequent stroke is the percentage change of CBF following an acetazolamide challenge.7,83 Perfusion CT is a useful method for documenting the serial change of cerebral hemodynamics over time.67 Figure 2 shows images obtained in a patient with moyamoya disease who received surgical revascularization and pre- and postoperative PCT. Postoperative PCT demonstrated improved cerebral hemodynamics in the middle cerebral artery (MCA) territory with increased CBF and decreased MTT compared with the preoperative PCT. Our experience also suggests that PCT may be useful to follow-up asymptomatic patients because cerebral perfusion changes on PCT usually precede clinical deterioration. It may also be interesting to assess the role of prophylactic revascularization in asymptomatic patients with worsening cerebral hemodynamics on PCT. Complete and serial documentation of higher cortical function is critical in the follow-up of these patients. In our limited experience, the PCT parameters showed good correlation with higher cortical function status.30,31

Assessment of Hemodynamic Status Following Surgical Revascularization

Perfusion CT can be used in several postoperative situations in the setting of surgical revascularization. In patients with external-internal carotid artery bypass or other surgical revascularization, PCT can help assess the patency of the bypass in conjunction with CTA, both immediately following surgery and during follow-up. Perfusion CT can also assess the residual CVR in the vascular territory supplied by the bypass, and has predictive value regarding the morbidity and long-term complications encountered in these patients (such as transient ischemic attack and stroke).56,78

Hyperperfusion Syndrome After Carotid Revascularization Surgery or Stent Placement

Hyperperfusion syndrome following carotid angioplasty with stenting or carotid endarterectomy is associated with significant morbidity and mortality. There is no reliable way to predict this syndrome, although older patients and patients with hypertension, with severe ipsilateral carotid stenosis, and with contralateral stenosis or occlusion, are at higher risk. Recently, PCT has been used to evaluate these patients, and a presenting regional CBV index greater than 0.15 and a time to peak index greater than 0.22 have been found to predict the risk of hyperperfusion syndrome.65,66 Interestingly, a recent study using MRI has shown that BBB breakdown is an important factor contributing to hyperperfusion syndrome.33 An obvious clinical application would be to use PCT to identify the high-risk patients so that judicious perioperative blood pressure control measures can be implemented to avoid this complication.

In addition, patients with carotid stenosis and impaired cerebral perfusion on PCT are more prone to develop ischemic lesions during ICA stenting. This suggests that not only embolic but also hemodynamic mechanisms play an important role in the risk of postprocedure stroke.36

Intracerebral Hemorrhage

The PCT technique is applicable not only for ischemic stroke, but also for hemorrhagic stroke. Perfusion CT is increasingly being used to investigate the perfusion of the perihematomal zone in patients with intracranial hematomas. Previous studies illustrated a gradient of decreasing cerebral perfusion toward the hematomas; that is, in the perihematomal zone.57,65 Whether cerebral ischemia is present in this “penumbral tissue” remains a topic of controversy. This issue is clinically important and has significant implications because the presence of ischemia would necessitate blood pressure management and possibly surgical management.21,85 However, recent studies have shown evidence against the presence of ischemia in the perihematomal zone.24,39 Instead, the hemodynamic compromise on PCT around the ICH is believed to be secondary to edema, increased local tissue pressure, and the presence of toxic blood products.24,25 Recently, Etminan et al.18 investigated early changes in cerebral perfusion after surgery for spontaneous ICH in 20 patients. They demonstrated impairment of cerebral hemodynamics in a preoperative imaging study and found distinct improvement of cerebral hemodynamics after surgery. Whether these early improvements after surgery can translate to decreased secondary injury after ICH remains to be elucidated.

Currently, use of PCT in patients with ICH is for investigational purposes only. However, PCT would serve as a valuable tool to evaluate the cerebral hemodynamic changes in these patients treated with different protocols, for instance in the setting of the ongoing clinical trials of blood pressure intervention in patients with ICH.

Aneurysmal SAH

Cerebral Ischemia and Vasospasm. Together with CTA, PCT is frequently incorporated into the CT workup of patients with SAH following an aneurysmal rupture, who are then at risk for developing vasospasm, to detect early cerebral ischemia and infarction. Cerebral vaso-
spasm is an important and devastating complication of aneurysmal SAH, occurs in 20%–30% of patients, and may result in cerebral infarction and poor outcome. Perfusion CT allows for noninvasive detection of vasospasm and the prediction of secondary cerebral infarction in patients with suspected vasospasm or delayed neurological deficit. Compared with transcranial Doppler ultrasonography, PCT is nonoperator dependent and provides quantitative data. It has been previously shown that the MTT as indicated by PCT is a sensitive and early predictor of secondary cerebral infarction in these patients.61 It has been reported that CBF and MTT have the highest overall diagnostic accuracy for determining vasospasm. Threshold values of 35 ml/100 g/min for CBF and 5.5-second MTT are suggested for delayed cerebral ischemia on the basis of the patient population utility method. Absolute threshold values may not be generalizable due to differences in scanner equipment and postprocessing methods.69 Perfusion CT is also useful in patient selection for intraarterial pharmacological treatment for vasospasm and also for monitoring treatment response.

In our center and many others, PCT is used in combination with transcranial Doppler ultrasonography to study patients with new neurological deficit after aneurysmal SAH. Areas of prolonged MTT values indicate territories with cerebral ischemia. Theoretically, the revers-
ibility of these ischemic injuries can be assessed based on whether CBV is increased or decreased, as in patients with ischemic stroke. The arteries supplying these territories are then evaluated by CTA for vasospasm. Computed tomography angiography is as sensitive and specific as diagnostic angiography. Conventional angiography is rarely needed for diagnostic purposes, and is instead reserved for patients who require intraarterial pharmacological treatment. In our opinion, PCT and CTA in combination with transcranial Doppler ultrasonography can obviate the need for unnecessary invasive angiography in selected lower-risk patients. In summary, PCT imaging can be used to identify patients with vasospasm or delayed cerebral ischemia after SAH and guide medical and endovascular therapy in these patients.

**Perfusion CT for Evaluation of Early Brain Injury and Patient Selection for Aggressive Treatment in Patients With Poor-Grade Aneurysmal SAH.** Previous studies have shown that early cerebral ischemia and infarction correlate with poor outcome. Early brain injury is the overall brain injury that occurs after SAH and involves apoptotic, inflammatory, and ischemic pathways. The activation of these pathways leads to increased intracranial pressure (ICP), decreased CBF, decreased cerebral perfusion, decreased cerebral oxygenation, BBB breakdown, cerebral brain edema, and neuronal death. In patients with poor-grade aneurysmal SAH, early brain injury is the primary cause of death and a key outcome predictor. In recent years there has been a paradigm shift from conservative to aggressive treatment in poor-grade aneurysmal SAH. It has been demonstrated that approximately 30% of these patients may eventually have good outcomes if they are treated aggressively. However, aggressive treatment of patients with irreversible brain damage is futile and may be a waste of medical resources. Currently, patient selection for aggressive treatment is still an area of uncertainty.

Sato et al. used DWI to evaluate patients with poor-grade aneurysmal SAH. They observed DWI abnormalities in 81.6% of the cases, and categorized these abnormalities into spotty and areal according to the size of these abnormalities. Coupled with apparent diffusion coefficient, the fate or the reversibility of these DWI abnormalities was assessed. These radiological characteristics were found to have a significant correlation with the outcome of these patients with poor grades.

In a retrospective study, Huang et al. included 49 patients with poor-grade aneurysmal SAH who were treated aggressively and underwent PCT. The study showed that perfusion abnormalities were present in 63% of patients. These abnormalities were then categorized into focal hypoperfusion, hemispheric, and global hypoperfusion (Fig. 3). Forty-four (56%) of the 78 total patients had favorable outcomes, and 34 (44%) had unfavorable outcomes, including 18 deaths (23%). Favorable outcomes among Grade IV patients were observed in 71%, whereas mortality among Grade V patients was 60%. Based on maps of CBF, CBV, and MTT, 18 patients had normal perfusion (37%), 18 patients had focal hypoperfusion (37%), 8 patients had hemispheric hypoperfusion (16%), and 5 patients had global hypoperfusion (10%). Most patients (89%) with normal cerebral perfusion had favorable outcomes and all 13 patients with hemispheric or global hypoperfusion had unfavorable outcomes. As a result, Grade IV patients with normal or focally abnormal perfusion appear to be good candidates for aggressive treatment, while Grade V patients with hemispheric or global hypoperfusion appear to be poor candidates. These results are analogous to those reported by Sato et al. Because there is a strong correlation between PCT and DWI, the consistent results observed in these two studies is logical. Perfusion CT and MRI are alternative imaging techniques to assess early brain injury. However, the greater availability and accessibility of PCT in the emergency or critical care setting compared with MRI needs to be considered, and PCT may be of more clinical value in the assessment of patients with early brain injury.

The causes of death and poor outcome in patients with poor-grade aneurysmal SAH include rebleeding, generalized cerebral edema, early cerebral ischemia, and/or infarction. Except for rebleeding, all these affect cerebral perfusion or hemodynamics, and can be monitored using PCT. A more comprehensive assessment in these patients would include perfusion, diffusion, oxygenation, and metabolism, but such assessment may be impractical to obtain in all patients in the critical care setting.

**Implications of PCT for TBI**

**Patients With Mild TBI and Postconcussion Syndrome**

In patients with mild TBI, PCT has been shown to be more sensitive than conventional CT in detecting cerebral contusions. Soustiel et al. studied 30 patients with cerebral contusions using PCT and found that admission CBV and CBF maps were highly compatible with the findings of follow-up noncontrast CT scans around 2 weeks after injury. Perfusion CT performed in the acute phase of mild TBI has been shown to detect perfusion abnormalities in patients with normal noncontrast CT scans. In a study of 74 patients with mild TBI without structural abnormalities on noncontrast CT scans, perfusion abnormalities were found to affect mostly the frontal and occipital regions and were shown to correlate with the severity of injury and outcome. In patients with a suboptimal outcome, defined by a Glasgow Outcome Scale Extended (GOSE) score less than 8 on follow-up, a significant decrease of CBF and CBV was present. Another group also demonstrated that in patients with mild TBI, posttraumatic amnesia was associated with cerebral perfusion abnormalities in the frontal region and the caudate nuclei.

In agreement with these studies, our data showed that patients with perfusion abnormalities in the frontal and temporal regions were at risk for prolonged post concussion syndrome and neurocognitive impairment. Although it has been long-believed that psychological factors play a major role in persistent post concussion syndrome (“miserable minority”), we found that a significant percentage of these patients have apparent perfusion abnormalities (unpublished data). In summary, early PCT has prognostic value in patients with mild TBI, especially if cerebral
Fig. 3. Contrast-enhanced CT scans (left column) and PCT scans (all other images) in patients with poor-grade aneurysmal SAH, obtained at admission. A: Normal cerebral perfusion. This patient had no intraparenchymal hemorrhage and no cerebral ischemia. Cerebral blood flow, CBV, and MTT were normal and symmetrical, and this patient had a favorable outcome. B: Focal hypoperfusion. This patient had a ruptured left MCA aneurysm and a thick sylvian fissure hematoma. The MTT was prolonged and CBF was decreased focally in the MCA territory around the hematoma. Cerebral blood flow in other territories in the left hemisphere was normal. The aneurysm was clipped and the hematoma evacuated, and the patient recovered with moderate disability (Glasgow Outcome Scale score = 4). C: Hemispheric hypoperfusion. This patient had a ruptured right MCA aneurysm and intracerebral hemorrhage. Cerebral blood flow and CBV were decreased and MTT was prolonged throughout the right hemisphere. Plain CT scans showed no signs of ischemia or infarction. Despite emergency hematoma evacuation, aneurysm clipping, and decompressive hemicraniectomy, the patient died. D: Global hypoperfusion. This patient had a ruptured right MCA aneurysm with an intracerebral hemorrhage and mild midline shift. Plain CT showed no signs of ischemia or infarction. Despite emergency hematoma evacuation, aneurysm clipping, and decompressive hemicraniectomy, the patient died. Perfusion CT showed global infarction with decreased CBF and CBV, and increased MTT. Reprinted with permission from Huang et al.: Neurosurgery 67:964–975, 2010.27
contusions are present or the initial Glasgow Coma Scale (GCS) score is less than 15.

Management of Patients With Moderate or Severe TBI: Cerebral Perfusion Pressure and Autoregulation

In patients with moderate or severe TBI, the cerebral perfusion pressure (CPP) protocol has long been the common practice to maximize the likelihood of positive outcome. Because PCT gives quantitative information regarding regional heterogeneity of cerebral perfusion and assesses cerebral autoregulation, PCT can add valuable information to the CPP protocol.

Early PCT results have been shown to correlate with long-term functional outcome of patients with TBI. Wintemark et al. evaluated 130 patients with severe TBI who received PCT evaluation as a part of the initial CT survey in a pilot study. These investigators found normal brain perfusion or hyperemia in patients with favorable outcome, and oligemia in patients with unfavorable outcome. Cerebral hypoperfusion detected by perfusion CT is associated with an unfavorable outcome and the number of arterial territories exhibiting low CBV has been shown to provide an independent predictor of outcome. Later, these authors studied 61 patients with severe TBI using early PCT and recommended that intermittent PCT measurements, in addition to continuous CPP measurement, could be used to provide more information than the standard CPP protocol alone. On the other hand, monitoring of brain tissue oxygen is an emerging tool and PCT assessment of a region of interest surrounding the monitoring probe in the brain tissue showed a significant correlation between MTT and brain tissue oxygen. Some also suggest that PCT performed before probe insertion can identify the high-risk region for tissue hypoxia, which the probe should target. As explained in the introduction, hemodynamic data obtained via PCT may provide assessment of the integrity of cerebral autoregulation and might therefore enable tailored hemodynamic therapy.

Perfusion CT performed in patients with TBI can quantify the degree of cerebral perfusion impairment related to cerebral edema, epidural hematoma, subdural hematoma, contusions, various types of brain herniation, and increased ICP. Hence, PCT can assess both primary and secondary injury in these patients compared with traditional noncontrast CT scans. This may explain the high correlation between PCT parameters and outcome. In a prospective study named the Contrast-Enhanced and Perfusion CT (CEPCT) study, we evaluated the clinical significance of early PCT in patients with moderate or severe TBI. We made several important observations in this study. First, PCT can be used to assess the salvageability of patients with poor GCS scores and/or uncal herniation. In a study period of 26 months, we only enrolled 16 patients with poor GCS scores and uncal herniation in whom CEPCT was performed before aggressive surgical treatment. In all cases, the attending neurosurgeon was present during the examination and transportation of these critically ill patients. Figure 4 shows a case with traumatic subdural hemorrhage and contusion hemorrhage with herniation. The preserved CBF and CBV in the midbrain were shown on the PCT map. The patient experienced a good neurological recovery after surgery. Similarly, among the 9 patients with uncal herniation and acceptable perfusion of the midbrain and thalamus, 5 had favorable outcomes and the other 4 had unfavorable outcomes after emergency surgery (Table 1). In contrast, all 7 patients with infarction of the midbrain and/or thalamus had unfavorable outcomes, even after emergency surgery (5 deaths and 2 persistent vegetative states; Table 1). Analogous to the PCT data for patients with poor-grade aneurysmal SAH, these data suggest that TBI patients with hemorrhagic or global severe hypoperfusion or infarction have poor outcomes, even after aggressive treatment. This early information is pivotal for both the surgeon and the family in terms of outcome prediction and clinical decision making.

In summary, PCT in patients with moderate or severe TBI may provide valuable information in terms of assessing autoregulation, prognosis, and perhaps patient selection for aggressive treatment. Further studies should confirm the role of PCT in terms of its value for therapeutic guidance.

Underlying Pathophysiology of Hemorrhage Progression: Importance of BBB Permeability, Contrast Enhancement, and Infarction Volume

The other interesting finding of our CEPCT study is that parenchymal contrast enhancement in the previously contused region predicts subsequent hemorrhage progression, clinical deterioration, and need for surgery. Therefore, patients with contrast enhancement are at risk for hemorrhage progression and should be monitored carefully or may be candidates for the investigational use of hemostatic agents (such as recombinant factor VIIa). Two clinical trials are now evaluating the use of factor VIIa in spot-sign–positive ICH patients; the “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) and the Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT). In a prospective study, we are now using the BBB permeability protocol to assess the relationship between increased permeability, brain edema, and hemorrhage progression in patients with TBI and ICH. Theoretically, patients with BBB breakdown may be at risk for these sequelae. Our concept is that patients with different degrees and extents of BBB dysfunction may need different CPP targets. The BBB map from PCT may be an invaluable tool for investigating and verifying our concept of “tailored blood pressure and/or CPP control.”

The underlying pathophysiology of hemorrhage progression and brain edema is an important and perplexing topic. It has been shown that a significant overlap in pathophysiology occurs in different neurosurgical diseases such as hemorrhage progression in spontaneous ICH or in traumatic contusion, and hemorrhagic transformation in ischemic stroke. Recently, the importance of increased BBB permeability has been shown as a necessary but not sufficient factor for hemorrhage progression. Other important factors include hypotension, coagulopathy, and intravascular thrombosis. The degree of increase in BBB permeability is also important; an increase in BBB permeability to a certain degree will lead to the diffusion of large
molecules such as albumin into the interstitial space and cause vasogenic edema. This diffusion and subsequent edema will increase the ICP, which presumably will, in turn, have a tamponade effect that will decrease the likelihood of hemorrhage progression. If the increase in BBB permeability is large enough for red blood cells and other blood cellular elements to pass, parenchymal contrast enhancement and/or the spot sign will occur and the patient might be at risk for hemorrhage progression later on. From our data and other studies, the extent of infarction is also highly correlated with hemorrhage progression. There is no doubt that BBB function plays a pivotal role in secondary injury. Further investigation of these factors may be able to bring answers to important questions, such as what is the proper blood pressure control for patients with ICH, stroke, or TBI; and what is the proper blood pressure control to salvage the reversibly damaged tissues, and achieve maximal functional recovery.

**Possible Surgical Implications of PCT**

Perfusion CT can help surgical planning in patients with TBI. The concepts of eloquent brain and functional preservation are rarely mentioned in the field of neurotrauma because most of these surgeries are life-saving in nature. Thanks to the recent advance of neuroanaesthesiology, surgical equipment and technique, and modern neurocritical care, the mortality rate of patients with moderate or severe TBI has decreased substantially during the last decade. However, functional outcome of the survivors is still poor, and efforts should be made to maximize the neurological recovery of these patients. The concept of surgery is simple in these patients; the

### TABLE 1: Perfusion CT data in TBI patients with uncal herniation undergoing decompressive surgery

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<thead>
<tr>
<th>Variable</th>
<th>Midbrain or Thalamus Infarction*</th>
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<tr>
<td>mortality rate (%)</td>
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</table>

* Infarction defined by decreased CBF, decreased CBV, and increased MTT.
† In the dichotomized outcome assessment, patients with good recovery and moderate disability were grouped as favorable outcome; patients with severe disability, vegetative state, or death were grouped as unfavorable outcome.

**Fig. 4.** Clinical application of PCT in a patient with TBI. This 53-year-old man suffered from right traumatic subdural hematoma and contusion hemorrhage, presenting with a GCS score of 3 and a right dilated pupil (with trace pupil response). Noncontrast axial head CT showed uncal herniation with brainstem compression (A) and severe midline shift (B). Follow-up CT 1 month after surgery showed decompression of the brainstem and resolution of contusion hemorrhage (C and D). Axial PCT completed with the initial noncontrast CT showed preserved CBF (E), CBV (F), and MTT (G) of the midbrain. After aggressive surgical treatment the patient recovered to E4M6V5 (GCS eye, verbal, and motor subscales) with a GOSE score of 7 (lower good recovery) at 6 months.
necrotic tissue should be debrided to provide room for the swollen brain, and the viable tissue (or tissue with reversible injury) should be preserved to maximize functional recovery. Accordingly, PCT can play a role in assessing tissue viability and the reversibility of tissue injury. We have found preoperative PCT especially useful in planning surgical management of cerebral contusions. During surgery, we remove all the area with irreversible injury and try to preserve the viable tissue, provided that the ICP is below 25 mm Hg after decompressive craniectomy. This concept is especially important in dealing with contusions around eloquent cortex.33 Whether this approach will lead to better functional recovery remains to be determined and needs to be confirmed in a larger cohort.

Intraoperatively, severe brain swelling is difficult to manage and death is usually imminent. In managing these patients, hemorrhage progression from cerebral contusion or contralateral epidural hematoma/subdural hematoma must be ruled out, either by intraoperative sonography or CT.29 If these are excluded, severe brain edema has occurred and selective lobectomy with or without ventricular drainage may be needed to achieve the goal of decompression. Similarly to the malignant stroke pattern previously described, patients with a large volume of infarction identified on PCT are at risk for this complication (and its inherent poor outcome), and lobectomy or the so-called strokectomy might be required because craniectomy may only provide limited decompression and may not be sufficient to lower the life-threatening elevation ICP. However, currently strokectomy remains controversial, and recent studies yielded equivocal results.11,41 If confirmed in a larger cohort, the information provided by PCT may be valuable for patient stratification, preoperative planning, and discussion with the family.

**Craniectomy and Cranioplasty**

Other surgery-related applications of PCT are the syndrome of the sinking skin flap and the motor trephine syndrome, encountered in patients with cranioplasty/craniectomy. Recent studies have shown that cranioplasty/craniectomy affects postural blood flow regulation, cerebrovascular reactivity, and cerebral glucose metabolism.

The syndrome of the sinking skin flap has been described as one of the causes of new neurological deterioration after craniectomy. It occurs in approximately 11% of patients after a large craniectomy.36,37 This syndrome consists of sunken skin above the bone defect, with neurological symptoms such as severe headaches, mental changes, focal deficits, or seizures. This syndrome may progress to paradoxical herniation as a result of the atmospheric pressure being greater than the ICP, and may have life-threatening consequences. Cranioplasty improves clinical and neurological symptoms of these patients. Perfusion CT studies of these patients after cranioplasty showed that the improvement of CBF occurs not only on the symptomatic side but also on the contralateral side.66

The motor trephine syndrome is also known as reversible monoparesis following decompressive hemislectomy, with similar pathophysiology to the syndrome of the sinking skin flap.30,81 In a study of 38 carefully followed patients with TBI, 10 patients (26%) experienced delayed contralateral upper-extremity weakness. This usually occurs 4.9 ± 0.4 months after craniectomy. Factors associated with this syndrome include ipsilateral contusions, abnormal CSF circulation, and longer intervals to cranioplasty repair. Once again, the motor weakness will improve after cranioplasty, and this is accompanied by improved cerebral hemodynamics on PCT. This phenomenon suggests that all patients who undergo craniectomy should undergo serial motor testing at frequent intervals until cranioplasty is performed. In addition, early cranioplasty repair may prevent this complication.81 In summary, PCT may be a tool to supplement the diagnosis of these syndromes and predict the reversibility of neurological symptoms after cranioplasty.

**Brain Death**

A final condition in which PCT may play a role is the diagnosis of brain death. Timely confirmation of brain death is very important as it allows families to make informed decisions about their loved ones. It avoids unnecessary use of aggressive therapeutic modalities and procedures. It may also improve organ procurement for transplant. Although the diagnosis of brain death is usually based on clinical criteria, difficulties ensue in sedated patients, patients with severe facial trauma, or those with metabolic problems, and supplementary studies are needed.

Computed tomography angiography is frequently performed as a supplementary test for brain death and might replace the standard 4-vessel angiography in these patients. Based on a study of 15 patients with brain death subjected to 2-phase CTA, Leclerc et al.44 proposed that lack of visualization of the cortical branches of the MCA and the internal cerebral vein are the best criteria for diagnosing brain death. Recently, studies have found PCT combined with CTA to be highly sensitive and specific for brain death diagnosis based on clinical and electroencephalogram findings.16,17,60 In a prospective study of 27 patients with clinically diagnosed brain death, CTA in addition to PCT was able to identify a lack of cerebral perfusion and intracranial circulation, and showed good correlation with the clinical and electroencephalography findings.8 In clinical examination as the reference standard, the sensitivity obtained for the CTA/PCT protocol was 89% and the specificity was 100%. In summary, CTA/PCT may be used due to its rapid, available, and noninvasive nature in patients with suspected brain death in whom confirmatory study is needed.

**Neurooncological Implications of PCT**

Perfusion CT can be used as an imaging biomarker in patients with brain tumor. The perfusion parameters obtained by using perfusion imaging have been used for tumor grading, prognosis, and treatment response.15,34 They also provide important data to differentiate nonneoplastic lesions from neoplasms, and recurrent tumor from a radionecrosis effect. Compared with MR perfusion imaging, PCT provides absolute quantification of the perfusion parameters and has no susceptibility artifacts due to hemorrhage (which may be present in postopera-
tive patients). However, MR perfusion imaging has been used more frequently because MRI is the standard imaging for brain tumor patients and does not have radiation exposure, which is of particular relevance in patients with brain tumors, who receive repeated follow-up imaging studies.

Using the dynamic contrast-enhanced imaging technique, both MR and CT imaging have been used to obtain parameters of tumor hemodynamics and pathophysiology. After the rapid administration of a contrast agent bolus and the acquisition of serial images at short intervals, an analysis that uses a pharmacokinetic model of the time dependence of contrast can generate parametric maps of tumor blood volume, blood flow, vascular permeability, and size of the extravascular extracellular space. Many of these parameters have been correlated with tumor grade, aggressiveness, treatment response, and prognosis. Figure 5 shows a case of metastatic tumor with increased CBV and CBF, elevated MTT, and abnormally elevated BBB permeability.12

**Tumor Blood Volume**

Measurement of tumor blood volume is a good surrogate marker for microvascular density, a measure of angiogenesis, and an important prognostic indicator in many cancers. Ellika et al. were able to differentiate low- and high-grade gliomas with a high sensitivity (85.7%) and specificity (100%) by using PCT and a CBV normalized relative to a normal-appearing contralateral white matter threshold of 1.92.15

**Tumor Vascular Permeability**

The endothelium of tumor blood vessels is relatively defective and leaky. Hypoxia or hypoglycemia that occurs in tumors with a high turnover rate increases the expression of vascular endothelial growth factor, which increases angiogenesis and permeability. The neoangiogenic vessels are immature and show increased permeability. These abnormal tumor vessels can be used as potential markers to assess tumor grade. Perfusion CT BBB measurements can be used to study the response of tumors to various therapies, especially antiangiogenic therapies.6 Assessment of the tumor vascular permeability can help in understanding the mechanism of the entry of therapeutic agents into the CNS and in developing methods to selectively alter the BBB to enhance drug delivery.62

Studies have shown that microvascular density could indicate total tumor vasculature, including both mature and immature vessels within the tumor. On the other hand, microvascular cellular proliferation could be an imaging biomarker of active angiogenesis and more immature and leaky blood vessels. A recent study that used image-guided biopsy specimens showed that CBV showed a stronger correlation with microvascular density, whereas permeability surface showed a stronger correlation with microvascular cellular proliferation.35

In summary, parameters obtained from PCT in patients with brain tumors may be used as imaging biomarkers for preoperative tumor grading and angiogenesis assessment. More specifically, these parameters may be valuable in differentiating between glioma grade (CBV and microvascular density, permeability surface, and microvascular cellular proliferation), in the assessment of angiogenesis heterogeneity (CBV for total tumor vascularity, permeability surface for active angiogenesis), in differentiating recurrent tumor from radiation necrosis (or pseudoprogression), and in differentiating gliomas from other nonneoplastic lesions and lymphomas.14 Perfusion CT could also be useful for treatment planning and response assessment.

**Limitations of PCT**

Now that we have reviewed the clinical applications of PCT, it is important to understand how PCT positions itself compared with other imaging techniques used to assess cerebral perfusion/metabolism.

Computed tomography and MRI share a lot of common features, both in terms of their results and their

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**Fig. 5.** Axial images obtained in a 61-year-old woman with a known metastatic gastric leiomyosarcoma. Noncontrast and postcontrast CT scans show a 3-cm, enhancing round mass, superficially located deep to the left supramarginal gyrus. This mass was histologically proved to be a dural metastasis. On PCT, the lesion demonstrated increased CBV and CBF, elevated MTT, and abnormally elevated BBB permeability. PS = permeability surface. Adapted with permission from Cianfoni et al.: J Neuroradiol 33:164–168, 2006.12
pitfalls. They do, however, have differences. Computed tomography involves radiation and an iodinated contrast medium. The radiation dose can be reduced to that of a noncontrast head CT (2 mSv) through the use of appropriate parameters (80 kVp and 100 mAs). Perfusion CT and CTA are safe even without measuring the serum creatinine level before injection of iodinated contrast material, provided that the patient does not have a history of renal failure.26 Modern CT scanners offer whole-brain coverage for PCT.68 Increased z-axis coverage can also be obtained for each bolus by using a toggling table technique, in which the CT scanner table moves back and forth, alternating between two different locations.84

Magnetic resonance imaging is preferable in younger patients because of the lack of ionizing radiation. Time-of-flight MR angiography and arterial spin-labeling perfusion imaging can be performed without administration of contrast material. Magnetic resonance angiography and perfusion-weighted MRI can also be performed using Gd contrast media; however, MR contrast material is contraindicated in patients with renal failure because of the risk of nephrogenic systemic fibrosis.7 Magnetic resonance im-

| TABLE 2: Summary of the clinical applications of PCT in neurosurgical diseases* |
|---------------------------------|---------------------------------|
| Diseases                        | PCT Applications                |
| cerebrovascular implications     |                                |
| acute ischemic stroke           | diagnosis; identification of penumbra & ischemic core, frequently used for patient selection for reperfusion therapy, especially in patients with wake-up stroke or onset greater than 3 hrs; identification of increased BBB permeability, these patients are at risk for malignant brain edema & hemorrhagic transformation; the possibility of clinical deterioration & subsequent craniectomy may be explained to the patient at early course |
| chronic cerebral ischemia       | diagnosis; assess the different stages of hemodynamic compromise & cerebrovascular reserve (via acetazolamide challenge) |
| moyamoya disease                | assess the different stages of hemodynamic compromise & cerebrovascular reserve (via acetazolamide challenge); predict the clinical course after op, risk of TIA & stroke |
| assessment following surgical revascularization | assessment of cerebral hemodynamics & revascularization together with CTA; predict the clinical course after op, risk of TIA & stroke |
| hyperperfusion syndrome after carotid intervention | diagnosis; predict the risk of hyperperfusion syndrome after carotid intervention & institute judicious blood pressure control to avoid this complication |
| intracerebral hemorrhage        | identification of ischemia or penumbra in the perihematoma region; may be used to assess the safety & efficacy of neuroprotective agents or blood pressure protocols |
| aneurysmal SAH                  | diagnosis of delayed ischemic neurological deficit or vasospasm & guide or assess the efficacy of endovascular or medical therapy for these complications; assessment of early brain injury & outcome prediction for poor grade subarachnoid hemorrhage patients |
| implications for TBI            |                                |
| mild TBI & postconcussion syndrome | more sensitive diagnosis & detection of cerebral confusion; outcome prediction in patients with GCS score < 15; hemodynamic compromise may be correlated with prolonged postconcussion syndrome or neurocognitive impairment |
| moderate to severe TBI          | assessment of autoregulation & BBB permeability, this new protocol may evaluate or validate the current CPP protocol, which relies on the hypothesis; outcome prediction & patient selection for aggressive management; possible surgical implications include identification of irreversibly injured tissue that will be removed during open operation; the BBB permeability protocol may identify patients at risk of hemorrhage progression & malignant brain edema at early stage |
| brain death                     | adjunctive diagnosis, high sensitivity & specificity when used with CTA |
| cranectomy & cranioplasty      | diagnosis of syndrome of the sinking skin flap or the motor trephine syndrome after craniectomy; validate hemodynamic improvement after cranioplasty |
| neurooncological implications   |                                |
| brain tumors                    | differentiation between glioma grade (CBV & microvascular decompression, PS, & microvascular cellular proliferation); assessment of angiogenesis heterogeneity (CBV for total tumor vascularity, PS for active angiogenesis); differentiation of recurrent tumor from radiation necrosis (or pseudoprogression); differentiation of gliomas from other nonneoplastic lesions & lymphomas; assessment of tumor vascular permeability & response to antiangiogenic therapy |

* PS = permeability surface.
Aging is contraindicated in patients with mechanical implants, electronically operated devices, or ferromagnetic hematostatic clips in the brain. Magnetic resonance imaging can be performed in selected patients with certain types of pacemakers using specific safety precautions.

One critical difference between PCT and MR perfusion imaging lies in the quantitative accuracy of perfusion measurements. Magnetic resonance perfusion imaging affords only semiquantitative measurements, while PCT offers quantitative measurements, validated by comparison with both xenon CT and PET. The key element supporting the use of CT in the initial evaluation of patients with suspected acute ischemic stroke is its wide availability, especially in the emergency setting.

Compared with other imaging modalities, PCT does not assess metabolism as PET or SPECT do. However, it provides quantitative data on cerebral perfusion and can be performed within a few minutes. Therefore, PCT is the perfusion imaging modality of choice when the condition of the patient is critical. In contrast, perfusion-weighted MRI does not provide quantitative results and is limited by susceptibility artifacts caused by blood products, frequently noted in patients after surgery. Compared with transcranial Doppler ultrasonography, PCT only provides a snapshot of the cerebral hemodynamic status, and not a continuous stream of live information. Another limitation is the limited spatial coverage that PCT provides, although this limitation will disappear soon with the introduction of wide detector coverage CT scanners.

As in all of medicine, the potential risks of any diagnostic test or therapeutic procedure (however rare) must be weighed against the very real benefits of limiting disability and preventing death. Perfusion CT imaging, when appropriately and correctly performed, is justified and provides valuable information that can substantially contribute to the safe management of acutely ill patients with a variety of neurosurgical conditions, as illustrated above.

**Future Perspectives**

With the advance of technology and imaging, and the advent of PET-CT, whole brain PCT, and intraoperative CTA/PCT, these techniques will expand their clinical applications to numerous neurosurgical diseases. With the increasing availability of combined PET-CT systems, PCT could represent an adjunct in selected patients undergoing PCT. This would allow simultaneous evaluation of cerebral perfusion and metabolism. Multimodal CT imaging consisting of noncontrast CT, CTA, and whole-brain PCT is increasingly used for acute stroke imaging. In a recent study of 10 patients with unruptured aneurysms, intraoperative CTA/PCT scanning was shown to be safe and feasible with a short acquisition time, minimal interference with the surgical workflow, and good diagnostic imaging quality. The use of this protocol in vascular neurosurgery is likely to grow. As previously mentioned, CBV is an important perfusion parameter in assessment of the reversible injury region. Recent technological advances allow parenchymal CBV to be measured in the angiography suite just before, during, or after an interventional procedure. Such tableside, flat-panel detector CT parenchymal CBV measurement in the angiography suite provides a feasible and helpful tool for peri-interventional neuroimaging.

**Conclusions**

Perfusion CT has diagnostic and prognostic value in a number of neurosurgical conditions (Table 2). It is the perfusion imaging modality of choice when the patient is in critical status. Its ability to assess the “reversibility” of injury has clinical implications, especially in patient selection and decision making. Further refinement of this imaging modality will shed light on the pathophysiological role of cerebral hemodynamic compromise, autoregulation, and BBB in numerous neurosurgical diseases.

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Address correspondence to: Max Wintermark, M.D., M.A.S., Neuroradiology Division, Department of Radiology, University of Virginia Medical Center, 1215 Lee St.–New Hospital, P.O. Box 800170, Charlottesville, VA 22908. email: max.wintermark@virginia.edu.