J.D. Eastwood
J.M. Provenzale

Cerebral blood flow, blood volume, and vascular permeability of cerebral glioma assessed with dynamic CT perfusion imaging

J.D. Eastwood (✉) · J.M. Provenzale
Division of Neuroradiology,
Department of Radiology,
Duke University Medical Center,
Box 3808, Durham, NC 27710, USA
E-mail: eastw004@mc.duke.edu
Tel.: +1-919-6847466
Fax: +1-919-6847157

Abstract We report dynamic CT perfusion imaging assessment of hemodynamics in a patient with a high-grade cerebral glioma and compare our results to those of previously published studies.

Introduction

There is a variety of imaging techniques for assessment of hemodynamic parameters (so-called perfusion imaging). They have been used primarily to assess cerebral ischemia, but have recently been applied to other cerebral disease processes.

Perfusion imaging of brain tumors has been shown to provide information about cerebral gliomas. Specifically, previous studies have shown that certain cerebral perfusion parameters, such as blood volume (CBV) and blood-brain barrier permeability, correlate well with tumor grade [1, 2, 3]. Perfusion imaging is also promising for distinguishing enhancement due to tumor from that due to radionecrosis [4].

Most prior studies comparing histologic features with perfusion parameters in brain tumors have used MRI [1, 2, 3, 4]. However, in certain situations (e.g., at institutions where perfusion MRI is not available, or in patients for whom MRI can not be performed), an alternative method for assessing tumor hemodynamics could be valuable.

A new method of measuring brain hemodynamics with CT has become available [5, 6, 7, 8]: dynamic CT perfusion imaging uses equipment available in most radiology departments to measure the first pass of a bolus of iodinated contrast medium. The method has been used to study the hemodynamics in acute stroke and has been validated in animal and human studies [5, 6, 8, 9]. We describe the use of dynamic CT perfusion imaging for assessment of hemodynamics in a patient with a high-grade glial neoplasm and compare our results to those of previous reports. To our knowledge, use of CT perfusion imaging to measure microvascular permeability in human cerebral glioma has not been reported previously.

Case report

A 71-year-old man was investigated for recent-onset confusion following placement of a cardiac pacemaker. Unenhanced CT showed right parietal lobe mass effect, and MRI could not be performed because of the pacemaker. CT angiography and a perfusion study were performed to determine whether the lesion was an infarct.

CT angiography of the circle of Willis was performed using 1 mm slice thickness and infusion of 150 ml iodinated contrast medium (370 mg/dl). No vascular stenosis or occlusion was seen. CT perfusion imaging was performed 5 min later using a multislice scanner. We obtained two contiguous 10 mm slices through the lesion using continuous (cine) scanning for a total of 45 s at 80 kVp and 190 mA. Tube speed was 1 revolution/s and data were

reconstructed at half-second intervals. We infused 40 ml iodinated contrast medium via an arm vein at 4 ml/s, beginning 5 s before the start of scanning.

Data were transferred to a workstation and analyzed using dedicated software. We calculated maps of CBV, cerebral blood flow (CBF), and permeability surface flow were calculated (Fig. 1). It was evident that the lesion was probably a tumor, as there was an enhancing nodule surrounded by an unenhancing region of low density. For each of the two contiguous slices, a reference CT image from the cine data set was segmented by an experienced neuroradiologist (J.D.E.). Regions of interest (ROI) were drawn by hand to delineate the part of the lesion that showed contrast enhancement and the region of low density in the white matter surrounding it. Care was taken to exclude as far as possible areas of presumed necrosis within the enhancing tumor. Thus, two ROI of differing size (one on each slice) contained enhancing tissue and two contained abnormal nonenhancing tissue. Because the lesion was in a site that would likely have contained both gray and white matter, both gray matter and white matter control regions in the contralateral hemisphere were studied. On each slice a hand-drawn gray-matter ROI corresponding to the location of the enhancing tumor was placed over the left parietal cortex over an area similar to that involved by tumor on the right. Similarly, ROI were placed on the left parietal white matter immediately adjacent to the gray-matter ROI.

The analysis software allowed ROI drawn on the reference image to appear simultaneously on all the perfusion maps. We recorded the size of each ROI and the mean CBV, CBF, and permeability surface flow within it. The mean of each parameter was then computed for enhancing tissue, surrounding edema, and control regions by taking the weighted average of the values within the ROI on both slices. For example, the mean CBF for the enhancing part of the lesion was found by averaging the values within the ROI encircling the enhancing part of the lesion on both slices after taking into account the area of each ROI.

Fig. 1a–d CT and haemodynamic data. **a** Reference image from the cine CT perfusion data set following infusion of contrast medium for CT angiography shows an enhancing lesion in the right parietal lobe srrounded by a region of low density in white matter (*arrows*). **b** Map of cerebral blood volume (CBV). Using region-of-interest (ROI) analysis, the enhancing part of the tumor (*large arrows*) contained 30% more blood than contralateral cortical tissue. **c** Map of cerebral blood flow (CBF) shows increased flow in the enhancing part of the tumor (*curved arrows*), 27% higher than that measured in normal cortical gray matter. The CBF of the region of surrounding low density (*arrowheads*) was 40% lower than in contralateral white matter. **d** Permeability surface flow map shows substantially increased blood-brain barrier permeability within the enhancing part of the tumor (*curved arrows*)
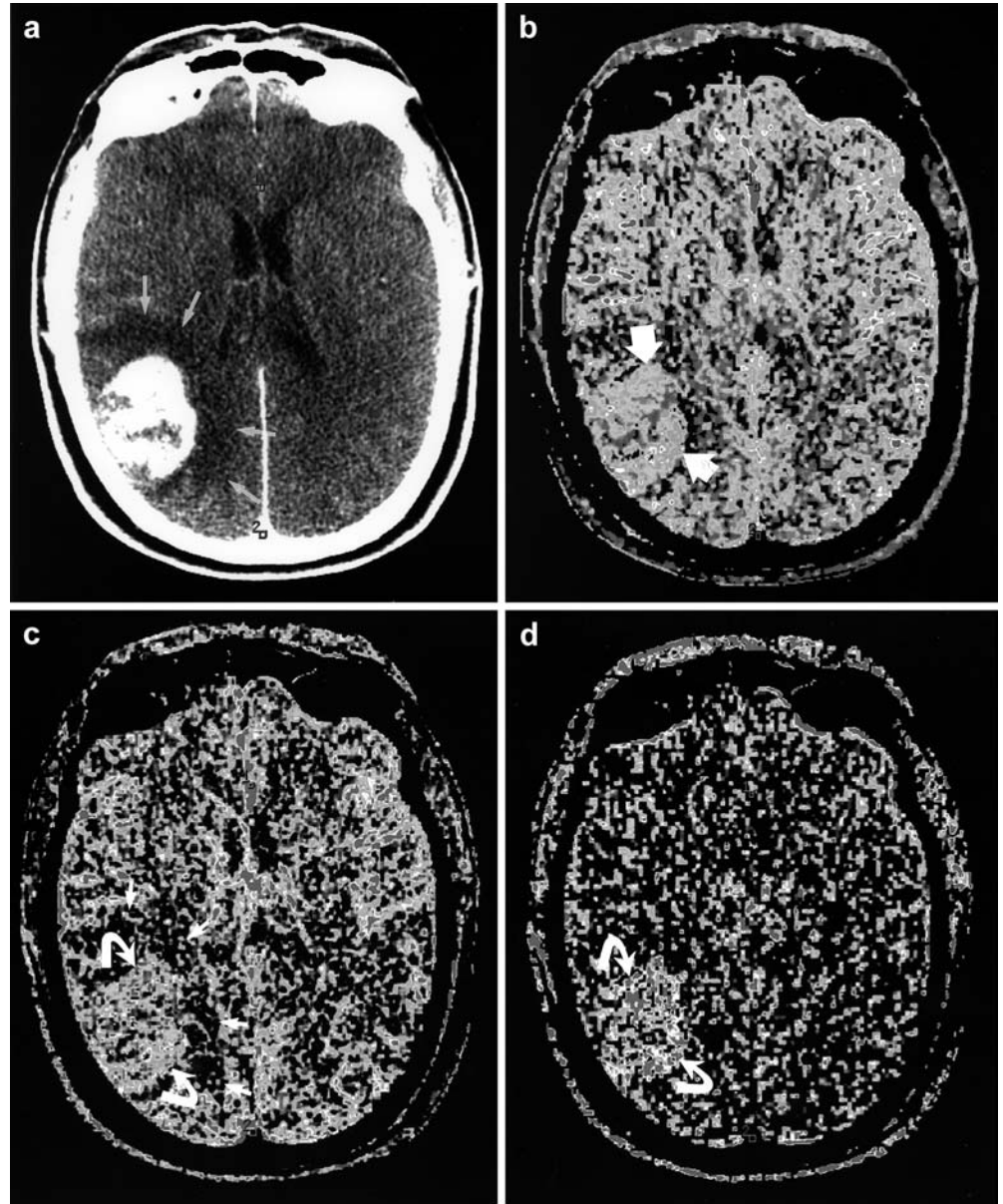
The mean CBV was 2.3 ml/100 g in the enhancing part of the tumor, 0.9 ml/100 g in the surrounding edema, 1.0 ml/100 g in the contralateral white matter, and 1.7 ml/100 g in the contralateral gray matter. The mean CBF was 70.8 ml/100 g/min in the enhancing part of the tumor, 16.0 ml/100 g/min in the surrounding edema, 24.1 ml/100 g/min in contralateral white, and 55.7 ml/100 g/min in contralateral gray matter. The mean permeability surface flow was 15.2 ml/100 g/min in the enhancing part of the tumor, 2.1 ml/100 g/min in the surrounding edema, 1.7 ml/100 g/min in contralateral white, and 2.4 ml/100 g/min in contralateral gray matter.

The patient underwent resection of the enhancing part of the tumor 2 days later which revealed grade IV astrocytoma (glioblastoma). He was discharged from the hospital 2 days after surgery in stable condition.

Discussion

Study of cerebral perfusion parameters in patients with brain tumors has been shown to provide information about histologic changes within tissue [1, 2, 3, 4]. For example, studies using perfusion MRI have shown that regional blood volume and microvascular permeability measurements correlate with tumor grade [1, 2, 3]. Accurate information about regional (focal) tumor grade could be clinically important for two reasons. First, accurate assessment of tumor grade can help in planning the most appropriate therapy. Second, cerebral gliomas are typically heterogeneous, with high- and low-grade regions within the same neoplasm [10]. Because overall tumor grade is assigned using the highest grade region the tumor contains, it is possible for a high-grade tumor to be misclassified because of sampling error [10]. Knowledge of the regions of tumor likely to be of high grade could help to direct biopsy and, thereby to decrease misclassification of tumors due to sampling error. It is possible that quantitative measurements of CBV, permeability, or both may be more accurate for prediction of tumor grade than simple assessment of contrast enhancement on T1-weighted images. This is a focus of ongoing research.

Dynamic CT perfusion imaging offers a widely available alternative to other methods for assessment of cerebral hemodynamics [5, 6, 7, 8, 11, 12]. Several studies have shown it to be highly promising for study of acute stroke [7, 11, 12]. CT-based imaging protocols have a number of advantages over other methods for study of acute stroke, including speed, availability, and sensitivity to hemorrhage. CT perfusion imaging may also have a role in other diseases processes because of advantages such as high spatial resolution and low cost.

The commercial algorithm we employed uses a deconvolution-based analysis which requires the operator to place small ROI over one artery and one vein to provide "input" functions [5, 6, 7, 8, 9]. CBF is found by comparing the arterial and tissue time-attenuation curves, after the former is corrected for volume averaging. Tissue CBV is then found by comparing the areas under the tissue and venous time-attenuation curves. In the case of a leaky blood-brain barrier, a slightly different deconvolution model is used [5]. The contrast medium is considered to include both intra- and extravascular components. Permeability surface flow is found by computing the fraction of contrast medium flow in the extravascular space. Once the permeability fraction is known, the corrected intravascular values of CBF and CBV can found. Compared with other methods of analysis, deconvolution methods are commonly thought to have a number of advantages such as accuracy and compatibility with slower infusion rates (e.g., 4–5 ml/s). One limitation of deconvolution analysis is operator dependence for placement of arterial and venous ROI.

Human studies using perfusion MRI in brain tumors have shown that high-grade tumors such as glioblastoma multiforme GBM typically have regionally increased relative CBV and increased microvascular permeability [1, 2, 3]. Our findings using CT perfusion imaging are thus in conformity with those reports.

Prior work by Cenic et al. [5] using a rabbit model of brain tumor has shown that CT perfusion imaging can provide information about hemodynamics in brain tumors. CBF, CBV and permeability surface flow were found to be higher in tumor than in the surrounding tissue or contralateral normal brain. Our findings of increased CBF, CBV, and permeability surface flow values in enhancing tumor compared with both peritumoral edema and contralateral tissue are thus in good agreement with the rabbit model. However, we did not find an increase in mean permeability, CBV and CBF in peritumoral edema. Possible reasons for this discrepancy may relate to differences in the host (rabbit versus human), tumor type (metastasis model versus primary tumor), or tumor histology.

Nabavi et al. [6] reported use of dynamic CT perfusion imaging in a one patient with a brain tumor. CBV and CBF were found to be increased within enhancing glioma, as in our study, but permeability surface flow was not measured. Roberts et al. [13] reported increased microvascular permeability in the enhancing portions of cerebral metastases using CT. Our finding of increased microvascular permeability within the enhancing portion of a glioma is thus in agreement with those found in metastases.

Although increased CBF and CBV were seen both in our study and that of Nabavi et al. [6], the absolute values of CBF and CBV were substantially different. Nabavi et al. [6] found that CBF and CBV within tumor were 155 ml/100 g/min and 5.5 ml/100 g, compared with 70.8 ml/100 g/min and 2.3 ml/100 g in our study. A number of factors could account for these differences. First, there could be differences in tumor vascularity (e.g., blood-vessel density) between the two tumors. Second, it is possible that a scaling factor could be

responsible. However, our control cortical CBF value (55.7 ml/100 g/min) was similar to that reported by Nabavi et al. [6] (52.1 ml/100 g/min), so it is unlikely that simple scaling is responsible. Finally, the lower tumor CBF and CBV seen in our study could reflect more accurate correction for the effects of leakage of contrast medium from blood vessels. Leakage across the blood-brain barrier causes overestimation of CBF and CBV if not accurately corrected for [5]. The commercial algorithm we used permits quantitative measurement of vascular permeability and also provides values of CBF and CBV corrected for the effects of vascular permeability.

One possible limitation of our findings may be that the perfusion study was performed after infusion of contrast medium for the CT angiogram. In theory, the preexistence of contrast medium in the extravascular space of the tumor could result in decreased net flow from the intravascular to the extravascular space. This could cause underestimation of microvascular permeability flow. The method we used to decrease this effect was to wait for 5 min after the CT angiogram to allow for back-diffusion of contrast medium from the extra- to the intravascular space. We suggest ideally one should try to perform tumor permeability measurements without prior infusion of contrast medium.

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